(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 520 723 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification : **01.06.94 Bulletin 94/22**

(51) Int. Cl.[5] : **C07D 413/12,** C07D 471/04, C07D 413/14, A61K 31/40

(21) Application number : **92305704.6**

(22) Date of filing : **22.06.92**

(54) **Angiotensin II antagonists.**

(30) Priority : **25.06.91 GB 9113628**

(43) Date of publication of application : **30.12.92 Bulletin 92/53**

(45) Publication of the grant of the patent : **01.06.94 Bulletin 94/22**

(84) Designated Contracting States : **AT BE CH DE DK FR GB IT LI LU MC NL PT SE**

(56) References cited :
EP-A- 0 400 974
EP-A- 0 429 257
EP-A- 0 488 532
WO-A-91/07404

(73) Proprietor : **IMPERIAL CHEMICAL INDUSTRIES PLC**
Imperial Chemical House,
Millbank
London SW1P 3JF (GB)

(72) Inventor : **Bradbury, Robert Hugh**
Alderley Park
Macclesfield, Cheshire SK10 4TG (GB)
Inventor : **Thomas, Andrew Peter**
Alderley Park
Macclesfield, Cheshire SK10 4TG (GB)

(74) Representative : **Smith, Stephen Collyer et al**
ICI Group Patents Services Dept.
PO Box 6
Shire Park
Bessemer Road
Welwyn Garden City Herts, AL7 1HD (GB)

EP 0 520 723 B1

Description

This invention concerns novel heterocyclic derivatives and, more particularly, novel heterocyclic derivatives which possess pharmacologically useful properties in antagonising at least in part one or more of the actions of the substances known as angiotensins, and in particular of that known as angiotensin II (hereinafter referred to as "AII"). The invention also concerns pharmaceutical compositions of the novel compounds for use in treating diseases or medical conditions such as hypertension, congestive heart failure and/or hyperaldosteronism in warm-blooded animals (including man), as well as in other diseases or medical conditions in which the renin-angiotensin-aldosterone system plays a significant causative role. The invention also includes processes for the manufacture of the novel compounds and their use in treating one of the afore-mentioned diseases or medical conditions and for the production of novel pharmaceuticals for use in such medical treatments.

The angiotensins are key mediators of the renin-angiotensin-aldosterone system, which is involved in the control of homeostasis and fluid/electrolyte balance in many warm-blooded animals, including man. The angiotensin known as AII is produced by the action of angiotensin converting enzyme (ACE) on angiotensin I, itself produced by the action of the enzyme renin on the blood plasma protein angiotensinogen. AII is a potent spasmogen especially in the vasculature and is known to increase vascular resistance and blood pressure. In addition, the angiotensins are known to stimulate the release of aldosterone and hence result in vascular congestion and hypertension via sodium and fluid retention mechanisms. Hitherto there have been a number of different approaches to pharmacological intervention in the renin-angiotensin-aldosterone system for therapeutic control of blood pressure and/or fluid/electrolyte balance, including, for example, inhibiting the actions of renin or ACE. However, there remains a continuing need for an alternative approach because of the side-effects and/or idiosyncratic reactions associated with any particular therapeutic approach.

In our published co-pending European Patent Applications, Publication Nos. 399731, 412848, 454831 and 453210 there are respectively disclosed certain imidazopyridine, quinoline, naphthyridine and pyridine derivatives which have AII antagonist activity.

We have now discovered that the compounds of the invention (set out below) surprisingly antagonise one or more of the actions of the substances known as angiotensins (and in particular of AII) and thus minimise the physiological effects associated with their presence in warm-blooded animals (including man) and this is the basis of the invention.

According to the invention there is provided a heterocyclic derivative of the formula I (set out hereinafter, together with the other chemical formulae identified by Roman numerals) wherein Q is selected from a group of the partial structural formula IIa, IIb, IIc or IId in which

ring B of formula IIa completes a benzene or pyridine ring;

R^1 and T^1 are independently selected from (1-8C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-4C)alkyl, phenyl, phenyl(1-4C)alkyl or substituted (1-4C)alkyl, the latter containing one or more fluoro substituents or bearing an (1-4C)alkoxy substituent;

R^2 and T^2 are independently selected from hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, phenyl or phenyl(1-4C)alkyl;

R^3 and R^4 are optional substituents on ring B independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano, nitro, fluoro(1-4C)alkoxy, hydroxy or hydroxy(1-4C)alkyl;

T^3 is selected from halogeno, (1-4C)alkoxy, amino, alkylamino and dialkylamino of up to 6 carbon atoms and any of the values defined for T^1;

T^4 is selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkyl containing one or more fluoro substituents, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, halogeno, cyano, nitro, carbamoyl, (1-4C)alkanoyl, N-alkylcarbamoyl and

di-(N-alkyl)carbamoyl of up to 7 carbon atoms, amino, alkylamino and dialkylamino of up to 6 carbon atoms, and a group of the formula $-A^1.B^1$ wherein A^1 is (1-6C)alkylene, a carbonyl group or a direct bond and B^1 is

(1) an unsubstituted phenyl or phenyl bearing one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl, nitro, hydroxy, carboxy, (1-4C)alkanoylamino, (1-4C)alkanoyl, fluoro(1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, carbamoyl, N-alkyl or di-(N-alkyl)carbamoyl of up to 7 carbon atoms, sulphamoyl, N-alkyl or di-(N-alkyl)sulphamoyl of up to 6 carbon atoms, (1-4C)alkoxycarbonyl, (1-4C)alkanesulphonamido, (1-4C)alkyl.$S(O)_n$- [in which n is zero, 1 or 2] and 1H-tetrazol-5-yl; or B^1 is

(2) a 5 or 6-membered saturated or unsaturated heterocyclic ring optionally bearing a (1-4C)alkyl group and containing a single heteroatom selected from oxygen, sulphur and nitrogen or containing two heteroatoms one of which is nitrogen and the other is oxygen, sulphur or nitrogen;

or T^3 and T^4 together form an (3-6C)alkenylene group, an (3-6C)alkylene group or an (3-6C)alkylene group in

which a methylene is replaced by carbonyl, provided that when T^3 and T^4 together form one of said latter three groups then T^2 is additionally selected from any of the previous values defined for T^4;
Y is oxygen or a group of the formula -NRb- wherein Rb is hydrogen, (1-4C)alkyl, (1-4C)alkanoyl or benzoyl;
linking group A of formula IIc is selected from -CH=CH-, -CH=CH-CO-, -CO-CH=CH-, $-CO-CH_2-CH_2-$, $-CH_2-CH_2-CO$, $-CH_2-CO$ and $-CO-CH_2-$;
E^1 is hydrogen, (1-8C)alkyl or trifluoromethyl;
E^2 is hydrogen, (1-8C)alkyl, halogeno, (1-4C)alkoxy, trifluoromethyl, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, (1-4C)alkanoyl, (1-4C)alkyl.$S(O)_m$- [in which m is zero, 1 or 2] or phenylsulphonyl;
E^3 is hydrogen, (1-8C)alkyl, (1-4C)alkoxy, halogeno or trifluoromethyl;
E^4 and E^5 are optional substituents on linking group A independently selected from (1-4C)alkyl, substituted (1-4C)alkyl containing one or more fluoro substituents, phenyl, pyridyl, alkoxy, halogeno, cyano, nitro, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, carbamoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl and (1-4C)alkanoyl;
L^1 is (1-8C)alkyl;
L^2 and L^3 are independently selected from hydrogen and (1-4C)alkyl;
X is oxygen, sulphur or a group of the formula -NRc wherein Rc is hydrogen or (1-4C)alkyl;
Ra is selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro;
Z is 1H-tetrazol-5-yl, carboxy or a group of the formula CF_3SO_2NH-; and wherein any of said phenyl moieties of R^1, R^2, T^1, T^2, T^3 or E^2 may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano and trifluoromethyl; or a non-toxic salt thereof.

It will appreciated that, depending on the nature of the substituents, certain of the formula I compounds may possess one or more chiral centres and may be isolated in one or more racemic or optically active forms. It is to be understood that this invention concerns any form of such a compound of formula I which possesses the afore-mentioned useful pharmacological properties, it being well known how to make optically active forms, for example by synthesis from suitable chiral intermediates, and how to determine their pharmacological properties, for example by use of the standard tests described hereinafter.

It is to be understood that generic terms such as "alkyl" include both straight and branched chain variants when the carbon numbers permit. However, when a particular radical such as "propyl" is given, it is specific to the straight chain variant, branched chain variants such as "isopropyl" being specifically named where intended. The same convention applies to other radicals.

A particular value for R^1, R^2, T^1 or T^2 where appropriate, include, by way of example,
for alkyl: methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl and hexyl;
for cycloalkyl: cyclopropyl, cyclopentyl and cyclohexyl;
for alkyl containing one or more fluoro substituents: fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and pentafluoroethyl;
for alkyl bearing an (1-4C)alkoxy substituent: 2-methoxyethyl and 2-ethoxyethyl;
for cycloalkyl-alkyl: cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and 2-cyclopentyl-ethyl;
for phenylalkyl: benzyl, 1-phenylethyl and 2-phenylethyl;
for alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; and
for alkenyloxycarbonyl: allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl and 3-methyl-3-butenyloxycarbonyl.

A particular value for T^3, T^4, or for T^2 when it is selected from a value for T^4, where appropriate, includes, by way of example, for alkyl: methyl, ethyl and propyl; for alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; for alkenyloxycarbonyl: allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl and 3-methyl-3-butenyloxycarbonyl; for halogeno: fluoro, chloro, bromo and iodo; for alkoxy: methoxy, ethoxy and propoxy; for alkyl containing one or more fluoro substituents: fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and pentafluoroethyl; for alkanoyl: formyl, acetyl and butyryl; for N-alkylcarbamoyl: N-methyl and N-ethylcarbamoyl; for di(N-alkyl)carbamoyl: N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl; for alkylamino: methylamino, ethylamino and butylamino; and for dialkylamino: dimethylamino, diethylamino and dipropylamino.

A particular value for A^1 when it is alkylene is, for example, methylene, ethylene or propylene.

Particular values for R^3, R^4 or an optional substituent on B^1 when it is phenyl bearing one or two substituents, where appropriate, include, by way of example,
for alkyl: methyl and ethyl; for alkoxy: methoxy and ethoxy; for halogeno: chloro, bromo and iodo; for alkanoylamino: formamido, acetamido and propanamido; for alkanoyl: formyl, acetyl and butyryl; for fluoroalkoxy: trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy and 3,3,3-trifluoropropoxy; for hydroxyalkyl: hydroxymethyl, 1-hydroxyethyl and 2-hydroxyethyl; for alkoxyalkyl: 2-methoxyethyl and 2-ethoxyethyl; for N-alkylcarba-

moyl: N-methyl and N-ethylcarbamoyl; for di(N-alkyl)carbamoyl: N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl; for N-alkylsulphamoyl: N-methyl and Nethylsulphamoyl; for di(N-alkylsulphamoyl: N,N-dimethylsulphamoyl and N,N-diethylsulphamoyl; for alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; for alkanesulphonamido: metanesulphonamido and ethanesulphonamido; for alkylthio: methylthio and ethylthio; for alkylsulphinyl; methylsulphinyl and ethylsulphinyl; and for alkylsulphonyl: methylsulphonyl and ethylsulphonyl.

A particular value for B^1 when it is a 5 or 6-membered saturated or unsaturated heterocyclic ring containing a single hetero atom selected from oxygen, sulphur or nitrogen includes, for example, a thienyl, furyl, pyrrolyl, pyrrolidinyl, pyridyl and piperidyl ring.

A particular value for B^1 when it is a 5 or 6-membered saturated or unsaturated heterocyclic ring containing two heteroatoms one of which is nitrogen and the other is oxygen, sulphur or nitrogen includes, for example, an imidazolyl, imidazolidinyl, pyrazolyl, pyrazolinyl, thiazolyl, thiazolinyl, oxazolyl, oxazolidinyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl and thiomorpholinyl ring.

A particular value for an alkyl group which may be present on B^1 when it is a saturated or unsaturated heterocyclic ring is, for example, methyl or ethyl.

A particular value for T^3 and T^4 when together they form (3-6C)alkylene is, for example, trimethylene, tetramethylene or pentamethylene; when together they form (3-6C)alkenylene is, for example, 1-propenylene, 2-propenylene, 1-butenylene, 2-butenylene or 3-butenylene; and when together they form (3-6C)alkylene wherein one of the methylene groups is replaced by a carbonyl group is, for example, 1-oxopropylidene, 3-oxopropylidene, 1-oxobutylidene or 4-oxobutylidene.

A particular value for Rb when it is alkyl is, for example, methyl or ethyl; and when it is alkanoyl is, for example, formyl, acetyl or propanoyl.

A particular value for E^1, E^2, E^3 or L^1 when it is alkyl is, for example, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl or hexyl.

A particular value for E^2 or E^3 when it is halogeno is, for example, fluoro, chloro, bromo or iodo; and when it is alkoxy is, for example, methoxy, ethoxy or propoxy.

A particular value for E^2 when it is alkoxycarbonyl is, for example, methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl; when it is alkenyloxycarbonyl is, for example, allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl or 3-methyl-3-butenyloxycarbonyl; when it is alkanoyl is, for example, formyl, acetyl or butyryl; when it is alkylthio is, for example, methylthio or ethylthio; when it is alkylsulphinyl is, for example, methylsulphinyl or ethylsulphinyl; and when it is alkylsulphonyl is, for example, methylsulphonyl or ethylsulphonyl.

Particular values for E^4 or E^5 include, by way of example, for alkyl: methyl and ethyl; for alkyl containing one or more fluoro substituents: fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and pentafluoroethyl; for alkoxy: methoxy and ethoxy; for halogeno: chloro, bromo and iodo; for alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; for alkenyloxycarbonyl: allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl and 3-methyl-3-butenyloxycarbonyl; and for alkanoyl: formyl, acetyl or butyryl; for N-alkylcarbamoyl: N-methylcarbamoyl aand N-ethylcarbamoyl; for di-(N-alkyl)carbamoyl: N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl; for alkylthio: methylthio and ethylthio; and for alkylsulphonyl: methylsulphonyl and ethylsulphonyl.

A particular value for L^2, L^3 or Rc when it is alkyl is, for example, methyl or ethyl.

A particular value for Ra or for an optional substituent which may be present on a phenyl moiety of R^1, R^2, T^1, T^2, T^3 or E^2 include, by way of example, for alkyl: methyl and ethyl; for alkoxy: methoxy and ethoxy; and for halogeno: chloro, bromo and iodo.

A value for R^1, T^1 or T^3 of particular interest is, for example, methyl, ethyl or propyl.

A value for R^2 of particular interest is, for example, hydrogen.

A value for T^2 of particular interest is, for example, hydrogen, alkoxycarbonyl or,when T^3 and T^4 form alkylene is, for example, halogeno.

A value for T^4 of particular interest is, for example, alkoxycarbonyl or halogeno.

A value of particular interest for T^3 and T^4 when together they form alkylene is, for example, trimethylene or tetramethylene.

A value for Y of particular interest is, for example, oxygen or a group of the formula -NRb- in which Rb is hydrogen.

A value for linking group A of formula IIc of particular interest is, for example, an optionally substituted group of the formula -CH=CH-, -CH=CH-CO- or $-CH_2-CH_2-CO-$.

A value of particular interest for E^1 is, for example, methyl, ethyl or propyl; for E^2 is, for example, hydrogen; for E^3 is, for example, methyl, ethyl or halogeno; for E^4 or E^5 is, for example, hydrogen, alkyl (such as methyl or ethyl), halogeno, phenyl, pyridyl, alkoxycarbonyl, carbamoyl, N,N-dialkylcarbamoyl, cyano, hydroxy, phenylthio or phenylsulphinyl.

A value of particular interest for L^1 is, for example, (1-4C)alkyl such as ethyl, propyl or butyl; and for L^2

and L^3 is, for example, methyl.

A value of particular interest for Q is, for example, 2-(1-4C)alkylquinolin-4-yloxy (such as 2-methylquinolin-4-yloxy or 2-ethylquinolin-4-yloxy), 2-(1-4C)alkyl-5,6,7,8-tetrahydroquinolin-4-yloxy (such as 2-methyl-5,6,7,8-tetrahydroquinolin-4-yloxy or 2-ethyl-5,6,7,8-tetrahydroquinolin-4yloxy), 2,6-di-(1-4C)alkyl-3-halogenopyrid-4-ylamino (such as 2,6-dimethyl-3-chloropyrid-4-ylamino, 2,6-dimethyl-3-iodopyrid-4-ylamino, 2,6-diethyl-3-chloropyrid -4-ylamino or 2,6-diethyl-3-iodopyrid-4-ylamino), 2,6-di-(1-4C)alkyl-4-halogeno-1H-pyrrolo[3,2-c] pyrid-1-yl (such as 2,6-dimethyl-4-chloro-1H-pyrrolo[3,2-c]pyrid-1-yl), 5,7-di-(1-4C)alkyl-2-oxo-1,2-dihydro-1,6-naphthyridin-1-yl (such as 5,7-dimethyl-2-oxo-1,2-dihydro-2-oxo-1,6-naphthyridin-1-yl or 5,7-diethyl-2-oxo-1,2-dihydro-2-oxo-1,6-naphthyridin-1-yl), 5,7-di-(1-4C)alkyl-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-1-yl (such as 5,7-dimethyl-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-1-yl or 5,7-diethyl-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-1-yl), 2-(1-4C)alkyl-3H-imidazo[4,5-b]pyrid-3-yl (such as 2-butyl-3H-imidazo[4,5-b]pyrid-3-yl) or 2,5,7-tri-(1-4C)alkyl-3H-imidazo[4,5-b]pyrid-3-yl (such as 2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyrid-3-yl).

A preferred value for X is, for example, oxygen.

A preferred value for Ra is, for example, hydrogen.

A preferred value for Z is, for example, 1H-tetrazol-5-yl.

A combination of values of special interest is, for example, when R^1 and R^3 are both alkyl; when T^1 and T^3 are both alkyl; when T^1 is alkyl and T^3 together with T^4 form alkylene; or when E^4 and E^5 are both hydrogen.

A particular group of compounds of the formula I which are of interest comprises compounds of the formula I sa defined above but excluding those compounds wherein one or both of E^4 or E^5 is selected from phenyl, pyridyl, carbamoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or a non-toxic salt thereof.

Further particular groups of compounds of the invention comprise those compounds of the formula I in which Q constitutes:-

(1) a group of the partial structural formula IIa in which ring B, R^1, R^2, R^3 and R^4 have any of the values defined hereinbefore;

(2) a group of the partial structural formula IIb in which T^1, T^2, T^3, T^4 and Y have any of the values defined hereinbefore;

(3) a group of the partial structural formula IIc in which E^1, E^2, E^3, E^4, E^5 and linking group A have any of the values defined hereinbefore; and

(4) a group of the partial structural formula IId in which L^1, L^2 and L^3 have any of the values defined hereinbefore;

and wherein in each of said groups the variables X, Z and Ra have any of the values defined hereinbefore; together with the non-toxic salts thereof.

Sub-groups of compounds of the invention of special interest from within the groups of compounds of particular interest (1) to (4) above comprise those compounds of the formula I in which Q constitutes:-

(a) a group of the partial structural formula IIa wherein ring B together with the pyridine ring to which it is attached constitutes a quinoline ring;

(b) a group of the partial structural formula IIa wherein ring B together with the pyridine ring to which it is attached constitutes a pyrido-pyridine ring (that is a naphthyridine);

(c) a group of the partial structural formula IIb wherein Y is an oxygen atom;

(d) a group of the partial structural formula IIb wherein Y is a group of the formula -NH-;

(e) a group of the partial structural formula IIc wherein linking group A together with the nitrogen atom and pyridine ring to which it is attached constitutes a 1,6-naphthyridin-2(1H)-one or a 1,2,3,4-tetrahydronaphthyridin-2-one ring; and

(f) a group of the partial structural formula IIc wherein linking group A together with the nitrogen atom and pyridine ring to which it is attached constitutes a 1H-pyrrolo[3,2-c] pyridine ring;

and wherein in each of said groups R^1, R^2, R^3, R^4, T^1, T^2, T^3, T^4, E^1, E^2, E^3, E^4 and E^5, where present have any of the values defined above and the variables X, Z and Ra have any of the values defined hereinbefore; together with the non-toxic salts thereof.

Preferred compounds of the formula I from within those contained in groups (1), (2), (3) or (4) or within sub-groups (a), (b), (c), (d), (e) or (f) above are those wherein the group Q-CH_2- is attached at the position marked with an asterisk (*). Of these, those compounds in which X is oxygen are particularly preferred.

Compounds of the invention which are of particular interest include, for example, the specific embodiments set out hereinafter in the accompanying Examples. Of these, the compounds of examples 3 and 4 are of special interest and these compounds, or non-toxic salts thereof, are provided as a further feature of the invention.

It will be appreciated that the formula I compounds can form salts with suitable acids or bases. Particularly suitable non-toxic salts for such compounds include, for example, salts with bases affording physiologically acceptable cations, for example, alkali metal (such as sodium and potassium), alkaline earth metal (such as magnesium and calcium), aluminium and ammonium salts, as well as salts with suitable organic bases, such as with ethanolamine, methylamine, diethylamine or triethylamine, as well as salts with acids forming physiologically acceptable anions, such as salts with mineral acids, for example with hydrogen halides (such as hydrogen chloride and hydrogen bromide), sulphuric and phosphoric acid, and with strong organic acids, for example with p-toluenesulphonic and methanesulphonic acids.

The compounds of formula I may be obtained by standard procedures of organic chemistry well known in the art for the production of structurally analogous compounds. Such procedures are provided as a further feature of the invention and include, by way of example, the following procedures in which the generic radicals have any of the values given above, unless stated otherwise:

a) For those compounds in which Z is carboxy, a carboxylic acid derivative of the formula III, in which W is a protected carboxy group selected from (1-6C)alkoxycarbonyl (especially methoxy-, ethoxy-, propoxy- or t-butoxy-carbonyl), phenoxycarbonyl, benzyloxycarbonyl and carbamoyl, is converted to carboxy.

The conversion may be carried out, for example by hydrolysis, conveniently in the presence of a suitable base such as an alkali metal hydroxide, for example, lithium, sodium or potassium hydroxide. The hydrolysis is generally carried out in the presence of a suitable aqueous solvent or diluent, for example in an aqueous (1-4C)alkanol, such as aqueous methanol or ethanol. However, it may also be performed in a mixture of an aqueous and non-aqueous solvent such as water and toluene using a conventional quaternary ammonium phase transfer catalyst. The hydrolysis is generally performed at a temperature in the range, for example, 0 - 120°C, depending on the reactivity of the group W. In general, when W is carbamoyl, temperatures in the range, for example, 40 - 120°C are required to effect the hydrolysis.

Alternatively, when W is benzyloxycarbonyl the conversion may also be performed by hydrogenolysis, for example using hydrogen at 1-3 bar in the presence of a suitable catalyst, such as palladium on charcoal or on calcium sulphate, in a suitable solvent or diluent such as a (1-4C)alkanol (typically ethanol or 2-propanol) and at a temperature in the range, for example, 0 - 40°C.

Further, when W is t-butoxycarbonyl, the conversion may also be carried out by hydrolysis at a temperature in the range, for example, 0 - 100°C, in the presence of a strong acid catalyst, such as trifluoroacetic acid. The hydrolysis may either be performed in an excess of the acid or in the presence of a suitable diluent such as tetrahydrofuran, t-butyl methyl ether or 1,2-dimethoxyethane.

b) For those compounds of formula I wherein Z is tetrazolyl, a compound of the formula IV in which P^1 is a suitable protecting group, such as trityl, benzhydryl, trialkyltin (for example trimethyltin or tributyltin) or triphenyltin, affixed to a nitrogen of the tetrazolyl moiety, is deprotected.

The reaction conditions used to carry out the deprotection necessarily depend on the nature of the group P^1. As an illustration, when it is trityl, benzhydryl, trialkyltin or triphenyltin, the decomposition conditions include, for example, acid catalysed hydrolysis in a mineral acid (such as aqueous hydrochloric acid), conveniently in an aqueous solvent (such as aqueous dioxan, methanol or 2-propanol). Alternatively, a trityl or benzhydryl group may be removed by hydrogenolysis, for example as described in (a) above for conversion of a benzyloxycarbonyl to a carboxy.

Compounds of the formula IV wherein P^1 is trialkyltin or triphenyltin may be obtained, for example, by reaction of a nitrile of the formula IX with a trialkyltin azide, such as tributyltin azide, or triphenyltin azide respectively. The reaction is conveniently carried out in a suitable solvent or diluent, such as toluene or xylene, and at a temperature in the range, for example, 50-150°C. In a modified procedure, a formula I compound wherein Z is tetrazolyl may be obtained directly by in situ removal of the trialkyltin or triphenyltin group without prior isolation of the formula III compound, for example, by the addition of aqueous mineral acid or gaseous hydrogen chloride to the reaction mixture. Nitriles of the formula IX may be obtained, for example, by alkylation of a compound of the formula **Q.H** (or a tautomer thereof) with a nitrile of the formula I wherein **Hal.** stands for a suitable leaving group such as chloro, bromo, iodo, methanesulphonyloxy or p-toluenesulphonyloxy, using similar conditions to those used in process (c) described hereinafter. The necessary compounds of formula X may be made by standard procedures such as those illustrates in Scheme 11 or by analogy therewith. Alternatively, the nitriles of the formula IX may be obtained from stepwise conversion of a compound of formula I wherein Z is a carboxy group or a compound of the formula III under standard conditions. Additionally, a nitrile of the formula IX wherein Q is a group of the partial structural formula IIb in which Y is the group -NRb- and Rb is alkanoyl or benzoyl may be obtained from the corresponding compound wherein Rb is hydrogen by acylation or benzoylation under standard conditions.

It will be appreciated that procedures (a) and (b) may be carried out with a compound of the formula III or IV respectively in which one or more functional groups of Q and X are protected with suitable protecting

groups. For example, when X is an imino (-NH-) group it may be protected with a suitable nitrogen protecting group such as an acyl group (for example acetyl, trichloroacetyl or trifluoroacetyl) or an alkyloxycarbonyl group (for example tert-butyloxycarbonyl). The protecting groups may be removed either during the carrying out of procedure (a) or (b), dependent on the conditions employed, or subsequent thereto using conventional techniques. For example, a tert-butyloxycarbonyl group used to protect X when it is imino may be removed by base hydrolysis, using for example an alkali metal hydroxide (such as sodium hydroxide) in a suitable solvent (such as methanol or ethanol) and at a temperature in the range of 0 to 100°C, preferably 75°C to ambient temperature.

c) A compound of the formula **Q.H** (or a tautomer thereof) is alkylated with a compound of the formula V wherein **Hal.** stands for a suitable leaving group such as chloro, bromo, iodo, methanesulphonyloxy or p-toluenesulphonyloxy.

The reaction is preferably carried out in the presence of a suitable base, for example, an alkali metal alkoxide such as sodium or potassium methoxide, ethoxide or tert-butoxide, an alkali metal hydride such as sodium hydride, or an alkali metal carbonate such as sodium or potassium carbonate, or an organic base such as diisopropylethylamine or 4-dimethylaminopyridine. The reaction is conveniently carried out in a suitable solvent or diluent, for example, a (1-4C)alkanol such as methanol or ethanol, an ether such as tetrahydrofuran or dioxan, or a polar solvent such as N,N-dimethylformamide or N-methylpyrrolidone and at a temperature in the range, for example, 10 - 100°C. In carrying out process (c), about two molecular equivalents of a suitable base is generally required.

It will be appreciated that it may be necessary to carry out procedure (c) with a starting material of formula V and/or **Q.H** in which one or more functional groups present are protected with suitable protecting groups. It will also be appreciated that procedure (c) is suitable for the production of the starting materials of formula III for the reaction described in (a) above if a compound of the formula Va is used in place of a formula V compound. Similarly, using an analogous procedure, but starting with the appropriate compound of the formula VI, the starting materials of the formula IV may be obtained for procedure (b). The compounds of formula V may be using conventional procedures from compounds of the formula Va and VI, which themselves may be obtained as illustrated in Scheme 11 or by analogy therewith.

Many of the compounds of formula **Q.H** (or the tautomers thereof) are already known and the remainder can be made by analogy therewith using standard procedures of organic chemistry well known in the art, for example as described in standard works of heterocyclic chemistry such as that edited by Elderfield. Certain 4-quinolones are described in EPA, Publication No. 412848 and certain 4-naphthyridones are described in International Patent Application No. PCT/GB90/01776. Certain 4-pyridones are described in Monatshefte fur Chemie, 1969, 100, 132; J. Chem. Soc. (B), 1968, 866; Liebigs Ann. Chem., 1882, 1656; Heterocycles, 1982, 13, 239; and J. Am. Chem. Soc., 1974, 96(4), 1152. Certain 4-aminopyridines may be obtained as described in Tet. Lett., 1990, 3485 from intermediates obtainable as described in J. Het. Chem., 1989, 26, 1575 or European Patent No. 129408. Certain imidazo[4,5-b]pyridines are described in EPA 399731 and EPA 400974. Other compounds of the formula **Q.H** may be obtained as illustrated in Schemes 1 to 10, or by analogy therewith.

d) For those compounds of formula I wherein Z is a group of the formula CF_3SO_2NH-, a compound of the formula VII is reacted with trifluoromethanesulphonic acid anhydride.

The reaction is preferably carried out in the presence of a base, such as triethylamine, and conveniently in a suitable solvent or diluent, for example dichloromethane, and at a temperature in the range of -78°C to ambient temperature. The compounds of the formula VII may be obtained by alkylation of a compound of formula **Q.H** with a compound of the formula VIII (which itself may be obtained as shown in Scheme 11) using similar conditions to those of process (c) above, followed by reduction of the nitro group in the intermediate obtained, for example by conventional catalytic hydrogenation.

Whereafter, those compounds of formula I wherein Z is 1H-tetrazol-5-yl may be obtained by stepwise conversion of a compound of the formula I wherein Z is a carboxy group, or a compound of the formula III, into the corresponding nitrile under standard conditions, followed by reaction of the nitrile with an azide such as an alkali metal azide, preferably in the presence of an ammonium halide, and preferably in the presence of a suitable polar solvent such as N,N-dimethylformamide and at a temperature in the range, for example, 50 to 160°C.

Whereafter, when a non-toxic salt of a compound of formula I is required, it may be obtained, for example, by reaction with the appropriate base affording a physiologically acceptable cation, or with the appropriate acid affording a physiologically acceptable anion, or by any other conventional salt formation procedure.

Further, when an optically active form of a compound of formula I is required, one of the aforesaid processes may be carried out using an optically active starting material. Alternatively, the racemic form of a compound of formula I in which Z is an acidic group may be resolved, for example by reaction with an optically

active form of a suitable organic base, for example, ephedrine, N,N,N-trimethyl(1-phenylethyl)ammonium hydroxide or 1-phenylethylamine, followed by conventional separation of the diastereoisomeric mixture of salts thus obtained, for example by fractional crystallisation from a suitable solvent, for example a (1-4C)alkanol, whereafter the optically active form of said compound of formula I may be liberated by treatment with acid using a conventional procedure, for example using an aqueous mineral acid such as dilute hydrochloric acid.

Certain of the intermediates defined herein are novel, for example the compounds of the formula III, IV, IX and X, and are provided as a further feature of the invention.

As stated above, the compounds of formula I will have beneficial pharmacological effects in warm-blooded animals (including man) in diseases and medical conditions where amelioration of the vasoconstrictor and fluid retaining properties of the renin-angiotensin-aldosterone system is desirable, at least in part by antagonism of one or more of the physiological actions of AII. The compounds of the invention will thus be useful in the treatment of diseases or medical conditions such as hypertension, congestive heart failure and/or hyperaldosteronism in warm-blooded animals (including man), as well as in other diseases or medical conditions in which the renin-angiotensin-aldosterone system plays a significant causative role. The compounds of the invention may also be useful for the treatment of ocular hypertension, glaucoma, cognitive disorders (such as Alzheimer's disease, amnesia, senile dementia and learning disorders), as well as other diseases such as renal failure, cardiac insufficiency, post-myocardial infarction, cerebrovascular disorders, anxiety, depression and certain mental illnesses such as schizophrenia.

The antagonism of one or more of the physiological actions of AII and, in particular, the antagonism of the interaction of AII with the receptors which mediate its effects on a target tissue, may be assessed using one or more of the following, routine laboratory procedures:

Test A: This in vitro procedure involves the incubation of the test compound initially at a concentration of 100 micromolar (or less) in a buffered mixture containing fixed concentrations of radiolabelled AII and a cell surface membrane fraction prepared from a suitable angiotensin target tissue. In this test, the source of cell surface membranes is the guinea pig adrenal gland which is well known to respond to AII. Interaction of the radiolabelled AII with its receptors (assessed as radiolabel bound to the particulate membrane fraction following removal of unbound radiolabel by a rapid filtration procedure such as is standard in such studies) is antagonized by compounds which also bind to the membrane receptor sites and the degree of antagonism (observed in the test as displacement of membrane-bound radioactivity) is determined readily by comparing the receptor-bound radioactivity in the presence of the test compound at the specified test concentration with a control value determined in the absence of the test compound. Using this procedure compounds showing at least 50% displacement of radiolabelled AII binding at a concentration of 10^{-4} M are retested at lower concentrations to determine their potency. For determination of the IC_{50} (concentration for 50% displacement of radiolabelled AII binding), concentrations of the test compound are ordinarily chosen to allow testing over at least four orders of magnitude centred about the predicted approximate IC_{50}, which latter is subsequently determined from a plot of percentage displacement against concentration of the test compound.

In general, the compounds of formula I as defined above show significant inhibition in **Test A** at a concentration of about 50 micromolar or much less.

Test B: This in vitro test involves the measurement of the antagonist effects of the test compound against AII-induced contractions of isolated rabbit aorta, maintained in a physiological salt solution at 37°C. In order to ensure that the effect of the compound is specific to antagonism of AII, the effect of the test compound on noradrenaline-induced contractions may also be determined in the same preparation.

In general, the compounds of formula I as defined above show significant inhibition in **Test B** at a final concentration of about 50 micromolar or much less.

Test C: This in vivo test involves using terminally-anaesthetised or conscious rats in which an arterial catheter has been implanted under anaesthesia for the measurement of changes in blood pressure. The AII antagonistic effects of the test compound following oral or parenteral administration, are assessed against angiotensin II-induced pressor responses. To ensure that the effect is specific, the effect of the test compound on vasopressin-induced pressor responses may also be determined in the same preparation.

The compounds of formula I generally show specific AII-antagonist properties in **Test C** at a dose of about 50 mg/kg body weight or much less, without any overt toxicological or other untoward pharmacological effect.

Test D: This in vivo test involves the stimulation of endogenous AII biosynthesis in a variety of species including rat, marmoset and dog by introducing a diet of low sodium content and giving appropriate daily doses of a saluretic known as frusemide. The test compound is then administered orally or parenterally to the animal in which an arterial catheter has been implanted under anaesthesia for the measurement of changes in blood pressure.

In general compounds of formula I will show AII-antagonist properties in **Test D** as demonstrated by a significant reduction in blood pressure at a dose of about 50 mg/kg body weight or much less, without any overt

toxicological or other untoward pharmacological effect.

By way of illustration of the angiotensin II inhibitory properties of compounds of the formula I, the compound of Example 3 gave an IC_{50} of $2.8x10^{-7}M$ in Test A described above.

The compounds of formula I will generally be administered for therapeutic or prophylactic purposes to warm-blooded animals (including man) requiring such treatment in the form of a pharmaceutical composition, as is well known in the pharmaceutical art. According to a further feature of the invention there is provided a pharmaceutical composition comprising a compound of formula I, or a salt thereof, as defined above, together with a pharmaceutically acceptable diluent or carrier. Such compositions will conveniently be in a form suitable for oral administration (e.g. as a tablet, capsule, solution, suspension or emulsion) or parenteral administration (e.g. as an injectable aqueous or oily solution, or injectable emulsion).

The compounds of formula I may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as a beta-adrenergic blocker (for example atenolol), a calcium channel blocker (for example nifedipine), an angiotensin converting enzyme (ACE) inhibitor (for example lisinopril) or a diuretic (for example furosemide or hydrochlorothiazide). It is to be understood that such a combination therapy constitutes a futher aspect of the invention.

In general a compound of formula I (or a pharmaceutically acceptable salt thereof as appropriate) will generally be administered to man so that, for example, a daily oral dose of up to 50 mg/kg body weight (and preferably of up to 10 mg/kg) or a daily parenteral dose of up to 5 mg/kg body weight (and preferably of up to 1 mg/kg) is received, given in divided doses as necessary, the precise amount of compound (or salt) administered and the route and form of administration depending on size, age and sex of the person being treated and on the particular disease or medical condition being treated according to principles well known in the medical arts.

In addition to their aforesaid use in therapeutic medicine in humans, the compounds of formula I are also useful in the veterinary treatment of similar conditions affecting commercially valuable warm-blooded animals, such as dogs, cats, horses and cattle. In general for such treatment, the compounds of the formula I will generally be administered in an analogous amount and manner to those described above for administration to humans. The compounds of formula I are also of value as pharmacological tools in the development and standardisation of test systems for the evaluation of the effects of AII in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the continuing search for new and improved therapeutic agents.

The invention will now be illustrated by the following non-limiting Examples in which, unless otherwise stated:-

(i) concentrations and evaporations were carried out by rotary evaporation in vacuo;

(ii) operations were carried out at room temperature, that is in the range 18-26°C;

(iii) flash column chromatography was performed on Merck Kieselgel 60 (Art. no. 9385) obtained from E Merck, Darmstadt, Germany;

(iv) yields, where given, are intended for the assistance of the reader only and are not necessarily the maximum attainable by diligent process development;

(v) ^1H NMR spectra were normally determined at 200 MHz in $CDCl_3$ or-using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d, doublet;

(vi) all end-products had satisfactory microanalyse; and

(vii) the term "1H-tetrazol-5-yl" stands for "1H-1,2,3,4-tetrazol-5-yl".

EXAMPLE 1

1M Sodium hydroxide solution (5.0 ml) was added to a solution of methyl 2-[5-((2-ethyl-5,6,7,8-tetrahydroquinolin-4-yloxy)methyl)benzoxazol-2-yl]benzoate (A) (443 mg) in methanol (20 ml) and the solution was left to stand for 72 hours. Volatile material was removed by evaporation and the residue was dissolved in methanol (10 ml). Water (40 ml) was added and the solution was neutralised with 1M acetic acid (5 ml). The precipitated solid was collected by filtration, dried by azeotroping with ethanol and triturated with ether to gibe 2-[5-((2-ethyl-5,6,7,8-tetrahydroquinolin-4-yloxy)methyl)benzoxazol-2-yl]benzoic acid (152 mg), as a white powder, m.p. 229-231°C; NMR (d_6-DMSO): 1.2(t, 3H), 1.7-1.85(m, 4H), 2.55-2.8(m, 6H), 5.3(s, 2H), 6.8(s, 1H), 7.55(dd, 1H), 7.65-7.9(m, 6H); mass spectrum (+ve FAB, DMSO/methanol/m-nitrobenzyl alcohol (NBA)): 429 $(M+H)^+$; microanalysis, found: C, 70.7; H, 5.6; N, 6.1%; $C_{26}H_{24}N_2O_4.0.5H_2O$ requires: C, 71.2; H, 5.7; N, 6.4%.

The starting material (A) was obtained as follows:-

(i) A solution of 2-amino-p-cresol (7.4 g) and methyl 2-formylbenzoate (obtained as described in J. Chem. Soc. (C), 1969, 1818) (9.8 g) in ethanol (120 ml) was heated under reflux for 2 hours. The solvent was removed by evaporation and the residue recrystallised from hexane to give 2-hydroxy-5-methyl-N-(2-methoxycarbonylbenzylidene)aniline (B) (12.3 g), m.p. 82-83°C; NMR: 2.35 (s, 3H), 4.0(s, 3H), 6.9(d, 1H), 7.0(d, 1H), 7.05(br s, 1H), 7.15(d, 1H), 7.5-7.7(m, 2H), 7.95(dd, 1H), 8.2(dd, 1H), 9.45(s, 1H).

(ii) Lead tetraacetate (16.6 g) was added portionwise to a solution of compound B (8.1 g) in chloroform (150 ml) and the mixture was stirred for 2 hours. Insoluble material was removed by filtration and the filtrate was washed with water (3 x 50 ml), followed by saturated sodium chloride solution (50 ml), and then dried ($MgSO_4$). The solvent was removed by evaporation and the residue was purified by flash chromatography, eluting with ethyl acetate/hexane (1:9 v/v), to give methyl 2-(5-methylbenzoxazol-2-yl)benzoate (C) (5.2 g), as an oil; NMR: 2.5(s, 3H), 3.85(s, 3H), 7.2(dd, 1H), 7.45(d, 1H), 7.55-7.7(m, 3H), 7.75-7.8(m, 1H), 8.05-8.1(m, 1H).

(iii) N-Bromosuccinimide (2.35 g) and azo(bisisobutyronitrile) (60 mg) were added to a solution of compound C (3.2 g) in carbon tetrachloride (60 ml). The mixture was heated under reflux for 4 hours and then cooled to ambient temperature. Insoluble material was removed by filtration and the filtrate was concentrated. The residue was recrystallised from hexane to give methyl 2-(5-bromomethylbenzoxazol-2-yl)benzoate (D) (2.1 g), m.p. 92-95°C; NMR: 3.9(s, 3H), 4.65(s, 2H), 7.45(dd, 1H), 7.55(dd, 1H), 7.6-7.7(m, 2H), 7.8-7.85(m, 2H), 8.0-8.1(m, 1H).

(iv) 2-Ethyl-4(1H)-quinolone (obtained from aniline and methyl propionylacetate using an analogous procedure to that described in Org. Syn. 1955, Coll. Vol. III, pages 374 and 593, m.p. 178-181°C) (30 g) was catalytically hydrogenated over platinum oxide (3.0 g). The catalyst was removed by filtration throught diatomaceous earth and the filtrate was concentrated. Toluene (2 x 250 ml) was added to the residue and the solution re-evaporated. The resulting oil was triturated with ether to give 2-ethyl-5,6,7,8-tetrahydro-4-(1H)-quinolone (E) (22.6 g) m.p. 226-227°C; NMR: 1.2(t, 3H), 1.65-1.85(m, 4H), 2.5-2.7(m, 6H), 6.1(s, 1H), 12.3(br s, 1H).

(v) Sodium hydride (53 mg) was added to a solution of compound E (354 mg) in N,N-dimethylformamide (DMF) (10 ml). When evolution of hydrogen ceased compound D (692 mg) was added and the solution was left to stand for 20 hours. Water (40 ml) was added and the mixture was extracted with ethyl acetate (2 x 30 ml). The extracts were washed with water (30 ml), followed by saturated sodium chloride solution (30 ml), and dried ($MgSO_4$). The solvent was removed by evaporation and the residue purified by flash chromatography, eluting with methanol/dichloromethane (1:19 v/v), to give methyl 2-[5-(2-ethyl-5,6,7,8-tetrahydroquinolin-4-yloxy)methyl)benzoxazol-2-yl]benzoate (A) (730 mg), m.p. 122-124°C (after trituration with ether); NMR: 1.3(t, 3H), 1.7-2.0(m, 4H), 2.6-2.95(complex m, 6H), 3.9(s, 3H), 5.25(s, 2H), 6.6(s, 1H), 7.45(dd, 1H), 7.55-7.7(m, 3H), 7.8-7.9(m, 2H), 8.0-8.1(m, 1H).

EXAMPLE 2

Using an analogous procedure to that described in Example 1, but starting from methyl 2-[5-((5,7-dimethyl-2-propyl-3H-imidazo[4,5,-b]pyridin-3-yl)methyl)benzoxazol-2-yl]benzoate (A), there was obtained in 55% yield 2-[5-((5,7-dimethyl-2-propyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)benzoxazol-2-yl]benzoic acid, m.p. 150-160°C (softens from 120°C); NMR (d_6-DMSO): 0.9(t, 3H), 1.6-1.8(m, 2H), 2.5(2 x s, 6H), 2.8(t, 2H), 5.6(s, 2H), 6.95(s, 1H), 7.2(dd, 1H), 7.5(d, 1H), 7.6-7.7(m, 3H), 7.75-7.9(m, 2H); mass spectrum (positive chemical ionisation (+CI)): 441$(M+H)^+$; microanalysis, found: C, 68.7; H, 5.6; N, 11.9%; $C_{26}H_{24}N_4O_3.0.6H_2O.0.4[(C_2H_5)_2O]$ requires: C, 69.1; H, 6.1; N, 11.7%.

The starting material A was obtained as follows:-

Using an analogous procedure to that described in Example 1, part (v), but starting from 5,7-dimethyl-2-propylimidazo[4,5-b]pyridine (obtained as described in European Patent Application, Publication No. 400974), there was obtained in 53% yield methyl 2-[5-((5,7-dimethyl-2-propyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)benzoxazol-2-yl]benzoate (A), m.p. 131-132°C (from ether); NMR: 0.95(t, 3H), 1.7-1.35(m, 2H), 2.55(s, 3H), 2.6(s, 3H), 2.8(t, 2H), 3.8(s, 3H), 5.6(s, 2H), 6.9(s, 1H), 7.2(dd, 1H), 7.45(d, 1H), 7.55-7.65(m, 3H), 7.75-7.8(m, 1H), 8.0-8.05(m, 1H).

EXAMPLE 3

2-[5-((2-Ethyl-5,6,7,8-tetrahydroquinolin-4-yloxy)methyl)benzoxazol-2-yl]benzonitrile (A) (287 mg) was dissolved in 0.7M solution of tributyltin azide in toluene (5 ml) and the solution was heated under reflux for 20 hours. A saturated solution of hydrogen chloride in ethanol (5 ml) was added and the solution was left for 30 minutes. Volatile material was removed by evaporation and the residue was recrystallised from ethanol to give

2-ethyl-5,6,7,8-tetrahydro-4-[(2-(2-(1H-tetrazol-5-yl)phenyl)benzoxazol-5-yl)methoxy]quinoline hydrochloride, m.p. 209-211°C; NMR (d_6-DMSO): 1.3(t, 3H), 1.7-1.9(m, 4H), 2.55-2.65(m, 2H), 2.9-3.05(m, 4H), 5.55(s, 2H), 7.5(s, 1H), 7.55(dd, 1H), 7.7(d, 1H), 7.8-7.9 (m, 4H), 8.2-8.3(m, 1H); mass spectrum (+ve FAB, DMSO/NBA): 453 $(M+H)^+$, 410, 278.

The starting material (A) was obtained as follows:-

(i) A solution of 2-bromomethylbenzonitrile (39.2 g) in acetonitrile (200 ml) was added to a solution of silver nitrate (34.0 g) in acetonitrile (200 ml) and the solution was left to stand for 20 hours. The precipitated silver bromide was removed by filtration and volatile material was removed from the filtrate by evaporation. The residue was partitioned between ether (400 ml) and water (200 ml) and the organic layer was separated, washed with saturated sodium chloride solution (200 ml) and dried ($MgSO_4$). Volatile material was removed by evaporation to give O-(2-cyanophenyl)nitrate (32.4 g) as an oil. The oil was dissolved in ethyl acetate (300 ml) and the solution was cooled to 0°C. A solution of 1,8-diazabicyclo[5,4,0]undec-7-ene (27.7 g) in ethyl acetate (60 ml) was added at such a rate that the temperature did not exceed 5°C. The mixture was allowed to warm to 20°C and left for 30 minutes. 2M Hydrochloric acid (300 ml) was added and the organic phase was separated, washed with water (300 ml), followed by saturated sodium chloride solution (300 ml), and dried ($MgSO_4$). The solvent was removed by evaporation to give 2-formylbenzonitrile (B) (22.9 g) as a solid which was used without further purification; NMR: 7.7-7.9(m, 3H), 8.05(dd, 1H), 10.4(s, 1H).

(ii) A solution of 2-amino-p-cresol (9.8 g) and 2-formylbenzonitrile (10.5 g) in ethanol (160 ml) was allowed to stand for 20 hours. The precipitated solid was filtered off and washed with ethanol (30 ml) to give 2-hydroxy-5-methyl-N-(2-cyanobenzylidene)aniline (C) (3.1 g), m.p. 135-138°C; NMR: 2.35(s, 3H), 6.95(d, 1H), 7.1(dd, 1H), 7.2(s & br s, 2H), 7.55(dt, 1H), 7.7(dt, 1H), 7.8(dd, 1H), 8.1(dd, 1H), 8.9(s, 1H).

(iii) Using an analogous procedure to that described in Example 1, part (ii), but starting from compound C, there was obtained in 24% yield 2-(5-methylbenzoxazol-2-yl)benzonitrile (D), m.p. 142-146°C; NMR: 2.5(s, 3H), 7.25(dd, 1H), 7.5-7.9(m, 5H), 8.4(dd, 1H).

(iv) Using an analogous procedure to that described in Example 1, part (iii), but starting from compound D, there was obtained 2-(5-bromomethylbenzoxazol-2-yl)benzonitrile (E) as a solid, in 98% crude yield, which was used without further purification; NMR: 4.65(s, 2H), 7.5(dd, 1H), 7.6-8.0(m, 5H), 8.4(d, 1H).

(v) Using an analogous procedure to that described in Example 1, part (v), but starting from compound E, there was obtained in 52% yield 2-[5-((2-ethyl-5,6,7,8-tetrahydroquinolin-4-yloxy)methyl)benzoxazol-2-yl]benzonitrile (A), m.p. 160-162°C; NMR: 1.3(t, 3H), 1.7-2.0(m, 4H), 2.6-2.95(m, 6H), 5.25(s, 2H), 6.6(s, 1H), 7.5(dd, 1H), 7.6-7.9(m, 3H), 7.9-8.0(m, 2H), 8.44(dd, 1H).

EXAMPLE 4

Using an analogous procedure to that described in Example 3, but starting from 2-[5-((5,7-dimethyl-2-propyl-3H-imidazo [4,5-b]pyridin-3-yl)methyl)benzoxazol-2-yl]benzonitrile (A), there was obtained in 42% yield 5,7-dimethyl-2-propyl-3-[(2-(2-(1H-tetrazol-5-yl)phenyl)benzoxazol-5-yl)methyl]-3H-imidazo[4,5-b]pyridine hydrochloride, m.p. 178-182°C; NMR (d_6-DMSO): 0.95(t, 3H), 1.6-1.9(m, 2H), 2.6(s, 3H), 2.65(s, 3H), 3.2(t, 2H), 5.8(s, 2H), 7.4(s, 1H), 7.45(dd, 1H), 7.65(d, 1H), 7.75(d, 1H), 7.8-7.9(m, 3H), 8.2-8.3(m, 1H); mass spectrum (+ve FAB, DMSO/Glycerol (GLY)): 463 $(M-H)^-$, 188.

The starting material (A) was obtained as a foam in 46% yield using an analogous procedure to that described in Example 1, part (v), but starting from 5,7-dimethyl-2-propylimidazo[4,5-b]pyridine and 2-(5-bromomethylbenzoxazol-2-yl)benzonitrile; NMR: 1.0(t, 3H), 1.7-1.9(m, 2H), 2.6(s, 3H), 2.7(s, 3H), 2.8(t, 2H), 5.6(s, 2H), 6.9(s, 1H), 7.3(dd, 1H), 7.55-7.7(m, 3H), 7.75(dt, 1H), 7.9(dd, 1H), 8.35(dd, 1H).

EXAMPLES 5-9

Using an analogous procedure to that described in Example 3, but starting from the appropriate compound of formula IX which may be obtained by carrying out the procedure of Example 3, part (v) with the appropriate compound of formula **Q.H** in place of 2-ethyl-5,6,7,8-tetrahydro-4(1H)-quinolone, the following compounds of formula I may be obtained:-

(Example 5): 2,6-diethyl-3-iodo-4-[(2-(2-(1H-tetrazol-5-yl)phenyl)benzoxazol-5-yl)methylamino]pyridine hydrochloride, using 4-amino-2,6-diethyl-3-iodopyridine in Example 3, part (v), itself obtained as follows:-

(i) Methyl 4-amino-2,6-diethylpyridine-3-carboxylate (3.94 g), itself obtained using an analogous procedure to that described in Tet. Lett., 1990, 3485 but starting from 3-amino-2-pentenenitrile (obtained as described in J. Het. Chem., 1989, 26, 1575) and methyl propionylacetate, is added to a mixture of 2M sodium hydroxide solution (9.5 ml) and methanol (40 ml) and the mixture is heated at reflux for 16 hours.

The solution is cooled to ambient temperature and volatile material is removed by evaporation. The residue is partitioned between ethyl acetate and a mixture of 2M hydrochloric acid (9.5 ml) and water (20 ml). The aqueous phase is separated, water is removed by evaporation and the residue is extracted with ethyl acetate/methanol (1:1 v/v). The combined organic extracts are filtered and solvent is removed from the filtrate by evaporation to give 4-amino-2,6-diethylpyridine-3-carboxylic acid (3.46 g) as a yellow-brown foam; NMR (d_6-DMSO): 1.18(m,6H), 2.64(q,2H), 3.12(q,2H), 6.49(s,1H), 8.28(broad s,2H),; mass spectrum (chemical ionisation, ammonia): 195$(M+H)^+$.

(ii) 4-Amino-2,6-diethylpyridine-3-carboxylic acid (3.26 g) is heated at 220°C for 50 minutes. The residue is cooled to ambient temperature and purified by flash chromatography eluting with concentrated aqueous ammonia solution/dichloromethane/methanol (1:85:15 v/v) to give 4-amino-2,6-diethylpyridine (1.94 g) as a solid, m.p. 133-137°C; NMR ($CDCl_3$/d_6-DMSO): 1.24(t,6H), 2.68(q,4H), 4.48(broad s,2H), 6.27(s,2H); mass spectrum (chemical ionisation, ammonia): 151$(M+H)^+$.

(iii) 4-Amino-2,6-diethylpyridine (1.8 g) is added to a solution of iodine (3.1 g) and [bis(trifluoroacetoxy-)iodo]benzene (5.7 g) in a mixture of dichloromethane (70 ml) and methanol (20 ml) and the mixture is stirred for 16 hours. Solvent is removed by evaporation and the residue is partitioned between ethyl acetate and a mixture of saturated sodium metabisulphite solution (50 ml) and saturated sodium carbonate solution (150 ml). The organic phase is separated, washed with saturated sodium chloride solution and dried. Solvent is removed by evaporation and the residue is purified by flash chromatography eluting with dichloromethane/methanol (97:3 v/v) to give 4-amino-2,6-diethyl-3-iodopyridine (1.33 g) as a solid, m.p. 72-74°C; NMR ($CDCl_3$): 1.25(m,6H), 2.65(q,2H), 2.96(q,2H), 4.59(broad s,2H), 6.30(s,1H); mass spectrum (chemical ionisation, ammonia): 277$(M+H)^+$.

(Example 6): 2-ethyl-4-[(2-(2-(1H-tetrazol-5-yl)phenyl)benzoxazol-5-yl)methoxy]quinoline hydrochloride, using 2-ethyl-4(1H)-quinolone in Example 3, part (v).

(Example 7): 4-chloro-2,6-dimethyl-1-[(2-(2-(1H-tetrazol-5-yl)phenyl)benzoxazol-5-yl)methyl]-1H-pyrrolo[3,2-c]pyridine, using 4-chloro-2,6-dimethyl-1H-pyrrolo[3,2-c]pyridine in Example 3, part (v) (itself obtained using the method described in Tetrahedron, 1976, 32, 1383-1390).

(Example 8): 5,7-diethyl-1-[(2-(2-(1H-tetrazol-5-yl)phenyl)benzoxazol-5-yl)methyl]-1,6-naphthyridin-2(1H)-one hydrochloride, using 5,7-diethyl-1,6-naphthyridin-2(1H)-one in Example 3, part (v), itself obtained as follows:-

(i) Palladium (II) acetate (50 mg) and tri(2-methylphenyl)phosphine (50 mg) were added to a solution of 4-amino-2,6-diethyl-3-iodopyridine (1.3 g), ethyl acrylate (1.2 ml) and triethylamine (1.2 ml) in DMF (25 ml). The mixture was heated at 130°C for 2 hours and then allowed to cool. Volatile material was removed by evaporation and the residue was purified by flash chromatography, eluting with aqueous ammonia (density 0.88g/ml)/dichloromethane/methanol (1:200:20, v/v/v) to give ethyl-3-[(4-amino-2,6-diethyl)pyridin-3-yl]acrylate as an oil; NMR ($CDCl_3$): 1.15-1.45(m, 9H), 2.7(q, 2H), 2.8(q, 2H), 4.25(q, 2H), 4.5(broad s, 2H), 6.25(d, 2H), 7.75(d, 2H); mass spectrum (chemical ionisation, ammonia): 249 $(M+H)^+$.

(ii) A solution of ethyl-3-[(4-amino-2,6-diethyl)pyridin-3-yl]acrylate (600 mg) in dry methanol (10 ml) was added to a solution of sodium methoxide, prepared from sodium (500 mg) and dry methanol (30 ml), and the mixture was heated at reflux under an atmosphere of argon for 3 hours. Solvent was removed by evaporation and the residue partitioned between ethyl acetate and water. The aqueous phase was separated and extracted with ethyl acetate. The combined organic solutions were washed with saturated sodium chloride solution and then dried ($MgSO_4$). The solvent was removed by evaporation and the residue was triturated with ether to give 5,7-diethyl-1,6-naphthyridin-2(1H)one (310 mg), as a solid, m.p. 170-171°C; NMR ($CDCl_3$): 1.45(m, 6H), 2.85(q, 2H), 3.1(q, 2H), 6.7(d, 1H), 6.95(s, 1H), 8.05(d, 1H), 12.05(broad s, 1H): mass spectrum (chemical ionisation, ammonia): 203$(M+H)^+$.

(Example 9): 5,7-diethyl-1-[(2-(2-(1H-tetrazol-5-yl)phenyl)benzoxazol-5-yl)methyl]-1,2,3,4-tetrahydro-1,6-naphthyridin-2-one hydrochloride, using 5,7-diethyl-1,2,3,4-tetrahydro-1,6-naphthyridin-2-one in Example 3, part (v), itself obtained as follows:-

A solution of ethyl-3-[(4-amino-2,6-diethyl)pyridin-3-yl]acrylate (540 mg) in ethanol (30 ml) was catalytically hydrogenated over 30% palladium on carbon. When uptake of hydrogen ceased the catalyst was removed by filtration through diatomaceous earth. The filtrate was concentrated by evaporation and the residue was purified by flash chromatography, eluting with dichloromethane/methanol (9:1 v/v), to give 5,7-diethyl-1,2,3,4-tetrahydro-1,6-naphthyridin-2-one (380 mg), as a solid, m.p. 100°C; NMR ($CDCl_3$): 1.15-1.4(m,6H), 2.6-2.9(m,6H), 2.95(t,2H), 6.45(s,1H), 8.5(broad s,1H); mass spectrum (chemical ionisation, ammonia): 205$(M+H)^+$.

EXAMPLE 10

Using an analogous procedure to that described in Example 4 there may be obtained 2-ethyl-5,7-dimethyl-3-[(2-(2-(1H-tetrazol-5-yl)phenyl)benzoxazol-5-yl)methyl]-3H-imidazo[4,5-b]pyridine hydrochloride, starting from 2-[5-((2-ethyl-5,7,dimethyl-3H-imidazo [4,5-b]pyridin-3-yl)methylbenzoxazol-2-yl]benzonitrile, which itself may be obtained using the procedure described in Example 4 but replacing 5,7-dimethyl-2-propylimidazo[4,5-b]pyridine by 2-ethyl-5,7-dimethylimidazo[4,5-b]pyridine (obtained as described in European Patent application, Publication No. 400974).

EXAMPLE 11

Using an analogous procedure to that described in Example 4 there may be obtained 2-butyl-3-[(2-(2-(1H-tetrazol-5-yl)phenyl)benzoxazol-5-yl)methyl]-3H-imidazo[4,5-b]pyridine hydrochloride, starting from 2-[5-((2-butyl-3H-imidazo [4,5-b]pyridin-3-yl)methylbenzoxazol-2-yl]benzonitrile, which itself may be obtained using the procedure described in Example 4 but replacing 5,7-dimethyl-2-propylimidazo[4,5-b]pyridine by 2-butylimidazo[4,5-b]pyridine (obtained as described in Indian J Chem., Sec. B, 1978, 16B, 531).

EXAMPLE 12

(Note: all parts by weight)

The compounds of the invention may be administered for therapeutic or prophylactic use to warm-blooded animals such as man in the form of conventional pharmaceutical compositions, typical examples of which include the following:-

a) **Capsule** (for oral administration)

Active ingredient *	20
Lactose powder	578.5
Magnesium stearate	1.5

b) **Tablet** (for oral administration)

Active ingredient *	50
Microcrystalline cellulose	400
Starch (pregelatinised)	47.5
Magnesium stearate	2.5

c) **Injectable Solution** (for intravenous administration)

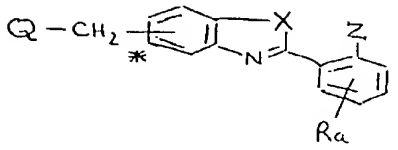
Active ingredient *	0.05 - 1.0
Propylene glycol	5.0
Polyethylene glycol (300)	3.0 - 5.0
Purified water	to 100%

d) **Injectable Suspension** (for intramuscular administration)

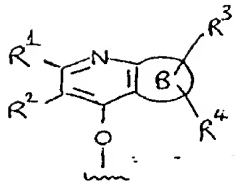
Active ingredient *	0.05 - 1.0
Methylcellulose	0.5
Tween 80	0.05
Benzyl alcohol	0.9
Benzalkonium chloride	0.1
Purified water	to 100%

Note: the active ingredient * may typically be an Example described hereinbefore and will conveniently be present as a pharmaceutically acceptable acid-addition salt, such as the hydrochloride salt. Tablets and capsules formulations may be coated in conventional manner in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating.

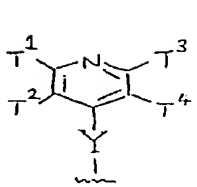
Chemical Formulae



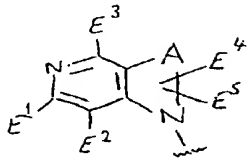
I



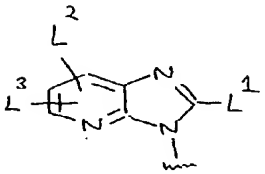
IIa



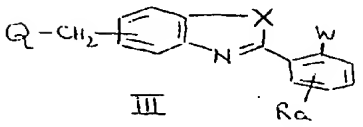
IIb



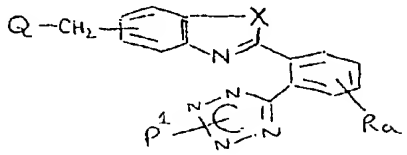
IIc



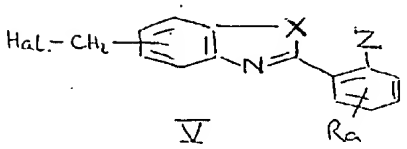
IId



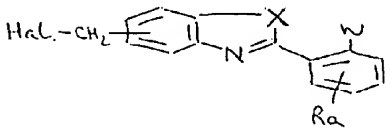
III



IV



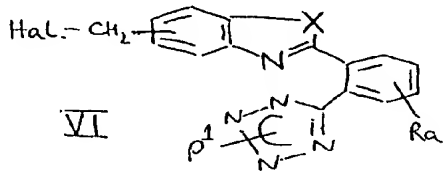
V



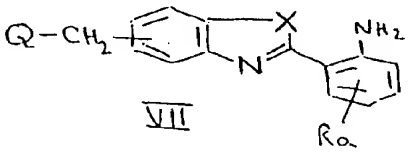
Va

Chemical Formulae

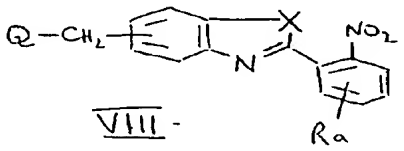
(continued)



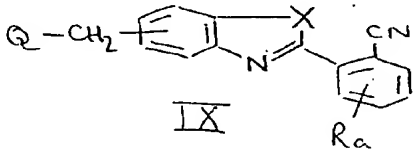
VI



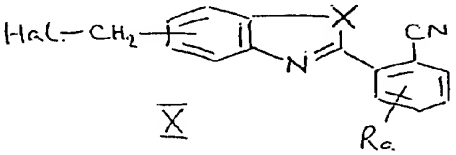
VII



VIII

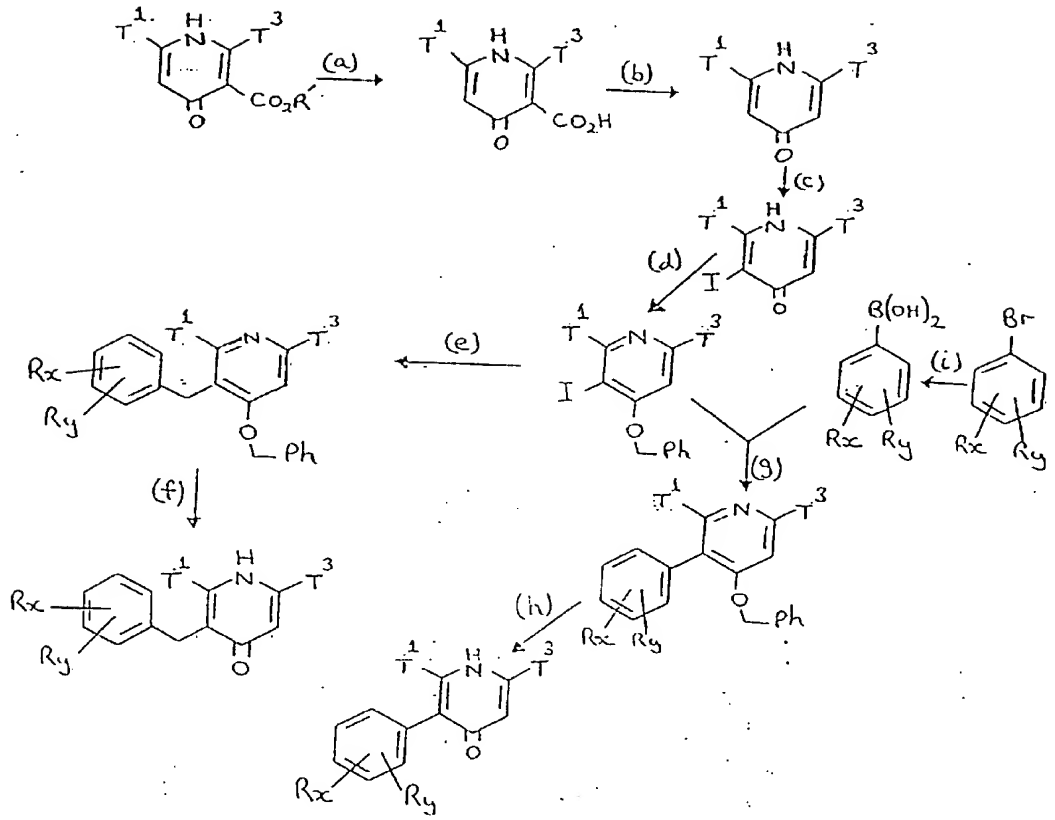


IX



X

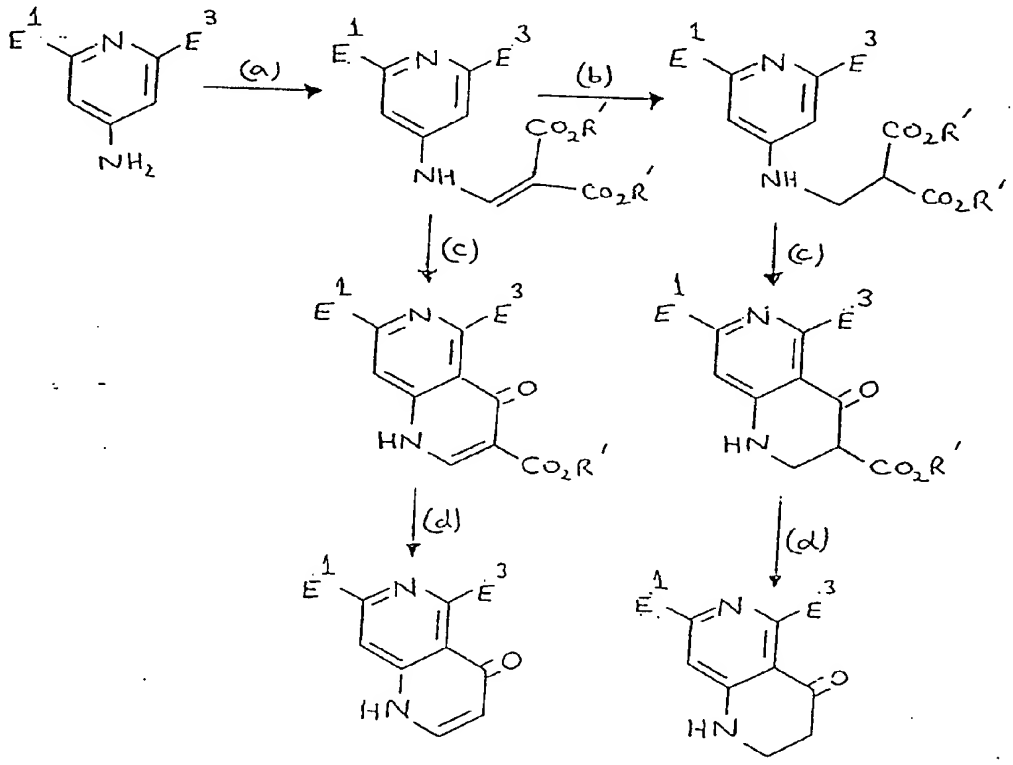
Scheme 1



Note: T^1 = T^3 = methyl or ethyl; Rx and Ry are optional substituents; Ph = phenyl; R' = lower alkyl

Reagents: a) NaOH, methanol, water, reflux
b) Sublimation at 250°C
c) Iodine, NaOH, water
d) $C_6H_5CH_2Cl$, NaH, DMF, 50°C
e) Product from (d) added to (Rx)(Ry)PhCH$_2$ZnBr in THF (from activated zinc, (Rx)(Ry)PhCH$_2$Br in THF), then $(Ph_3P)_4Pd$
f) hydrogenation over palladium on carbon, methanol
g) $(Ph_3P)_4Pd$, methanol, aq. $NaHCO_3$, toluene, reflux
h) ammonium formate, 10% palladium on carbon, methanol
i) tert-ButylLi/pentane; trimethyl borate/THF/-78°C; aq. HCl

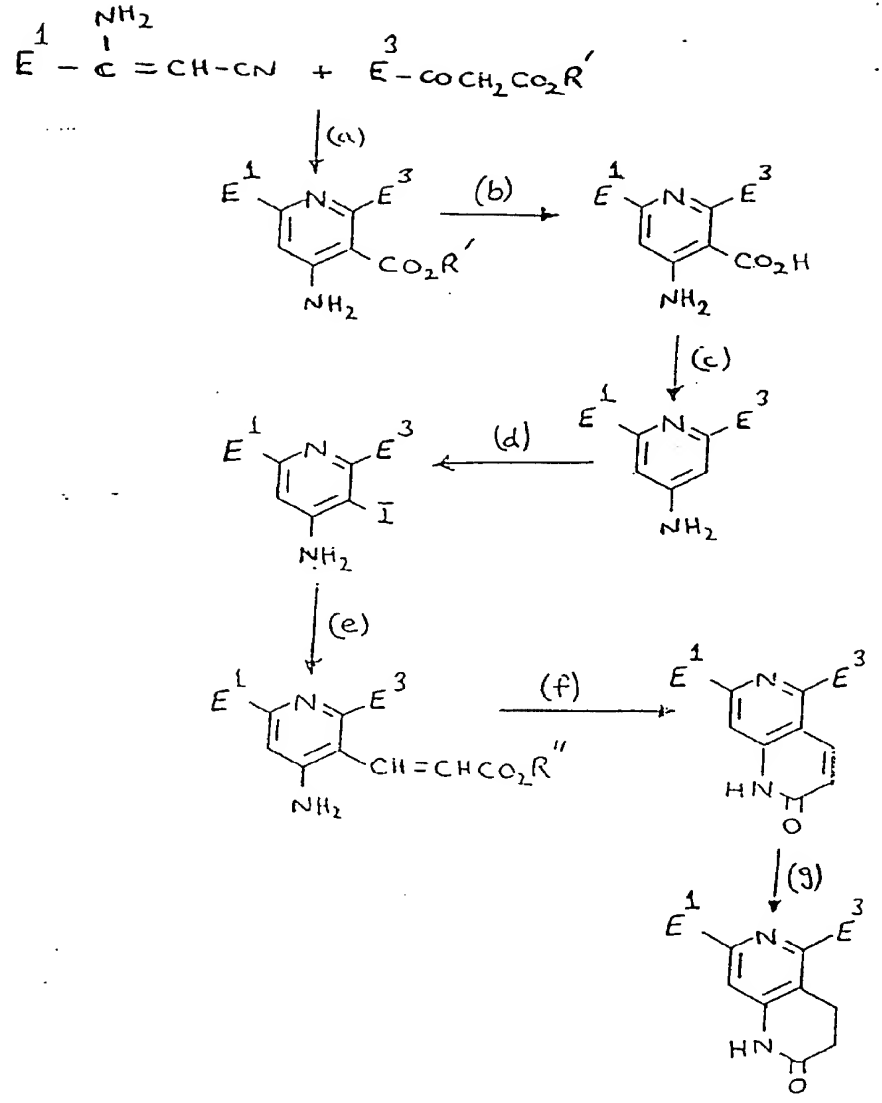
Scheme 2



Note: R' = lower alkyl

Reagents: a) $R'OCH{=}C(CO_2R')_2$, 110°C
b) hydrogen, Pd on C or PtO_2
c) Ph-Ph/Ph-O-Ph mixture, reflux
d) (i) NaOH; (ii) as for step (c)

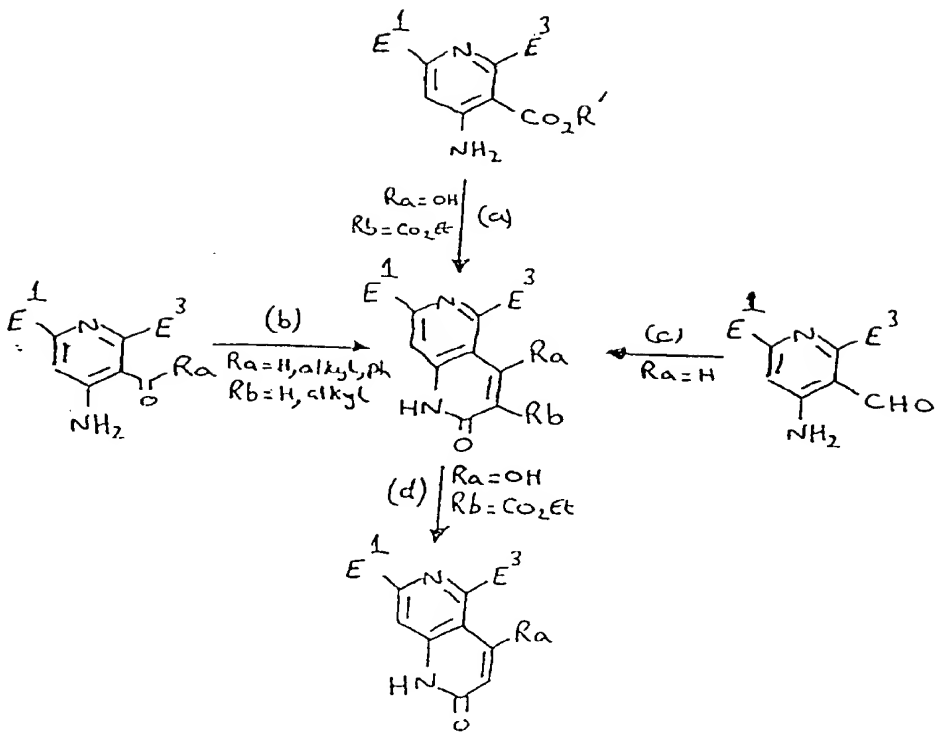
Scheme 3



Note: R' = lower alkyl ; R'' = lower alkyl

Reagents: a) $SnCl_4$, toluene, reflux
b) aqu. NaOH, methanol, reflux; then HCl
c) heat, 220°C
d) I_2, [bis(trifluoroacetoxy)iodo]benzene, CH_2Cl_2, methanol
e) Pd(II)acetate, tri(2-methylphenyl)phosphine, Et_3N, DMF, 130°C, $CH_2=CHCO_2R''$
f) $NaOCH_3$, methanol, reflux
g) hydrogen, palladium on carbon, acetic acid/ethanol, 20 atmospheres, 70°C

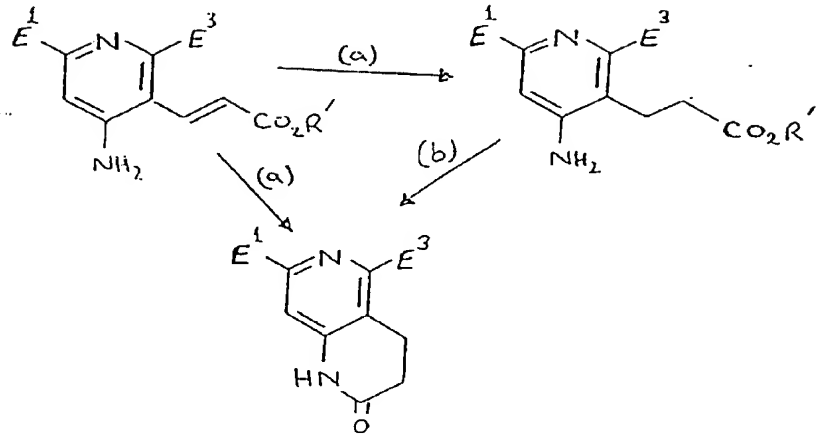
Scheme 1



Note: Et=ethyl; Ph=phenyl; R'=lover alkyl

Reagents: a) diethyl malonate, NaOEt, EtOH, 150°C, autoclave
b) $Ph_3P=C(Rb)CO_2Et$, xylene or toluene, reflux
c) $RbCH_2CO_2Et$ (e.g. $Rb=CO_2Et$, Ph, Pyridyl, CN, SPh), EtOH, piperidine, reflux
d) aqu.HCl, dioxan, reflux

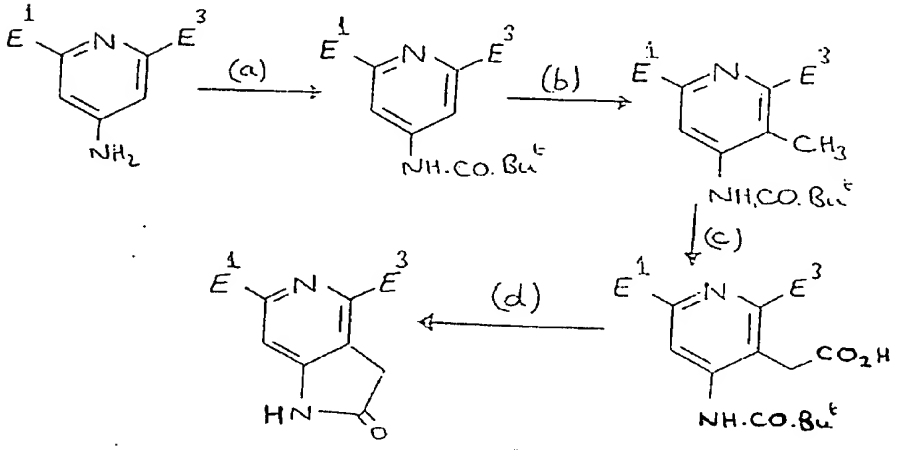
Scheme 5



Note: R' = lower alkyl

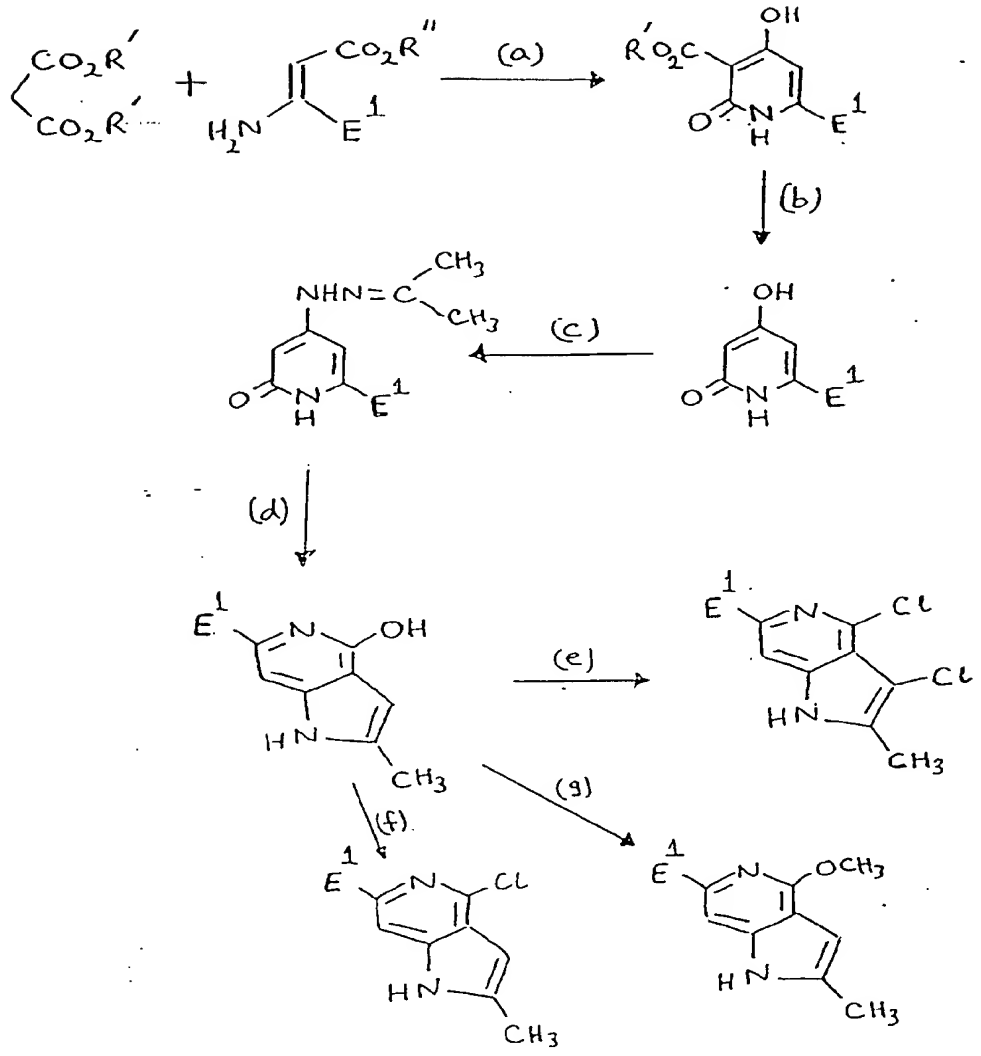
Reagents: a) hydrogen, Pd on C or PtO_2
b) heat

Scheme 6



Reagents: a) 1-(tert-butyl.CO)imidazole, toluene, heat
b) (i) tert-butyllithium (2 equivalents), -78°C, THF;
(ii) iodomethane
c) as (b)(i); then carbon dioxide
d) aqueous HCl, heat

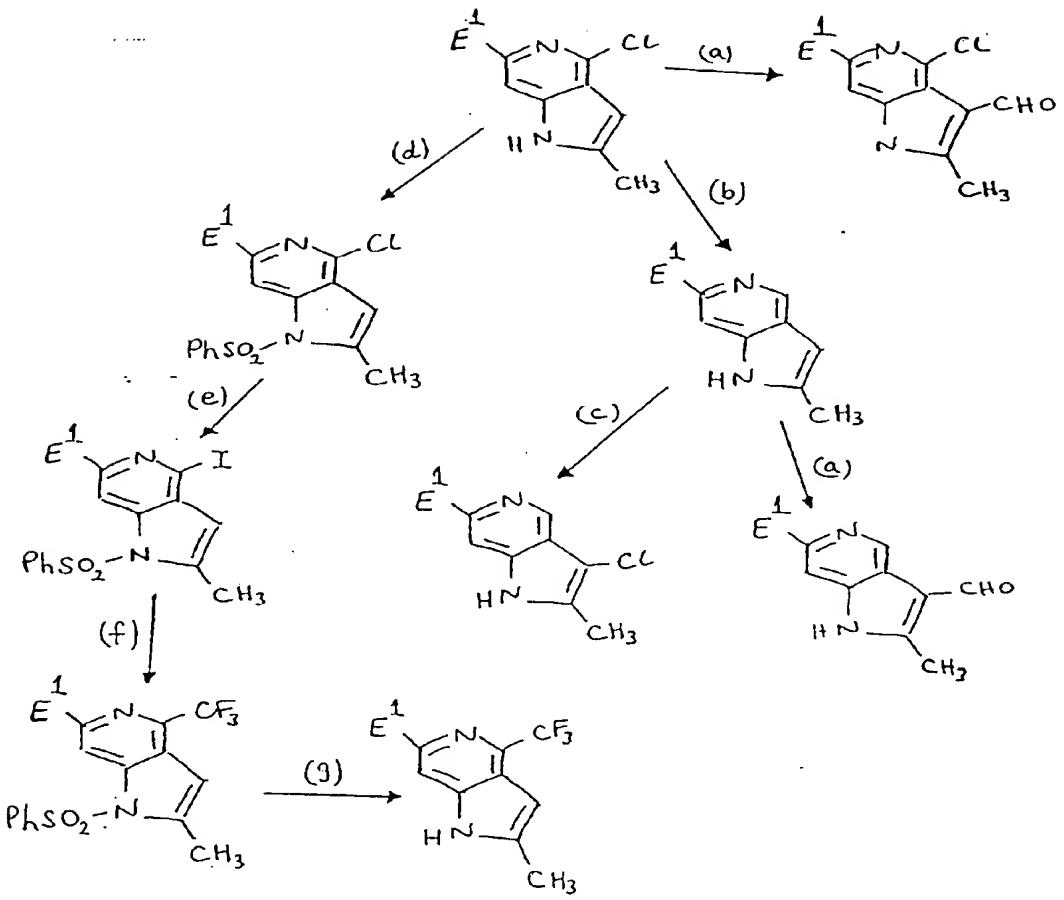
Scheme 7



Note: R' and R" = lower alkyl;

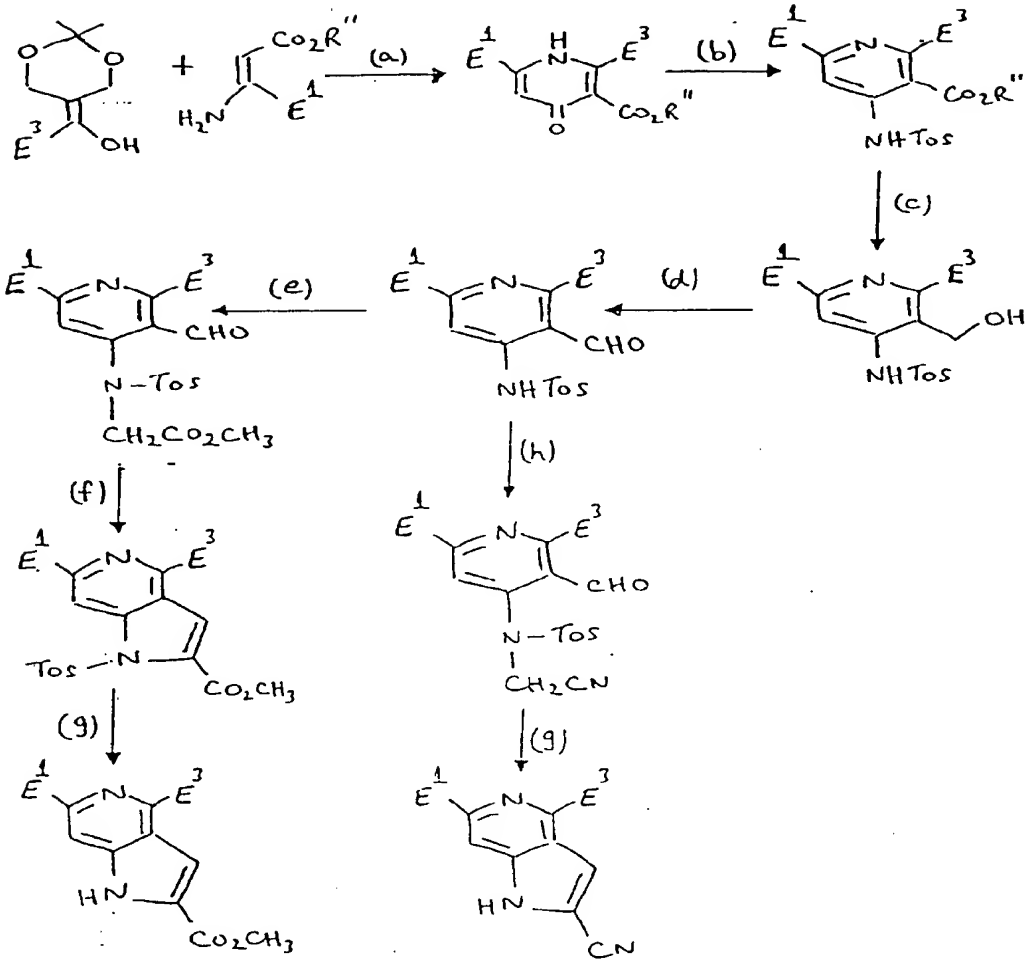
Reagents: (a) NaOMe, heat
(b) (i) NaOH (ii) HCl (iii) heat
(c) hydrazine hydrate, 2-ethoxyethanol, reflux; then acetone, reflux
(d) Ph-Ph/Ph-O-Ph mixture, reflux
(e) $POCl_3$, PCl_5, heat
(f) $POCl_3$ (freshly distilled), reflux
(g) $(CH_3)_3OBF_4$, dichloromethane

Scheme 8



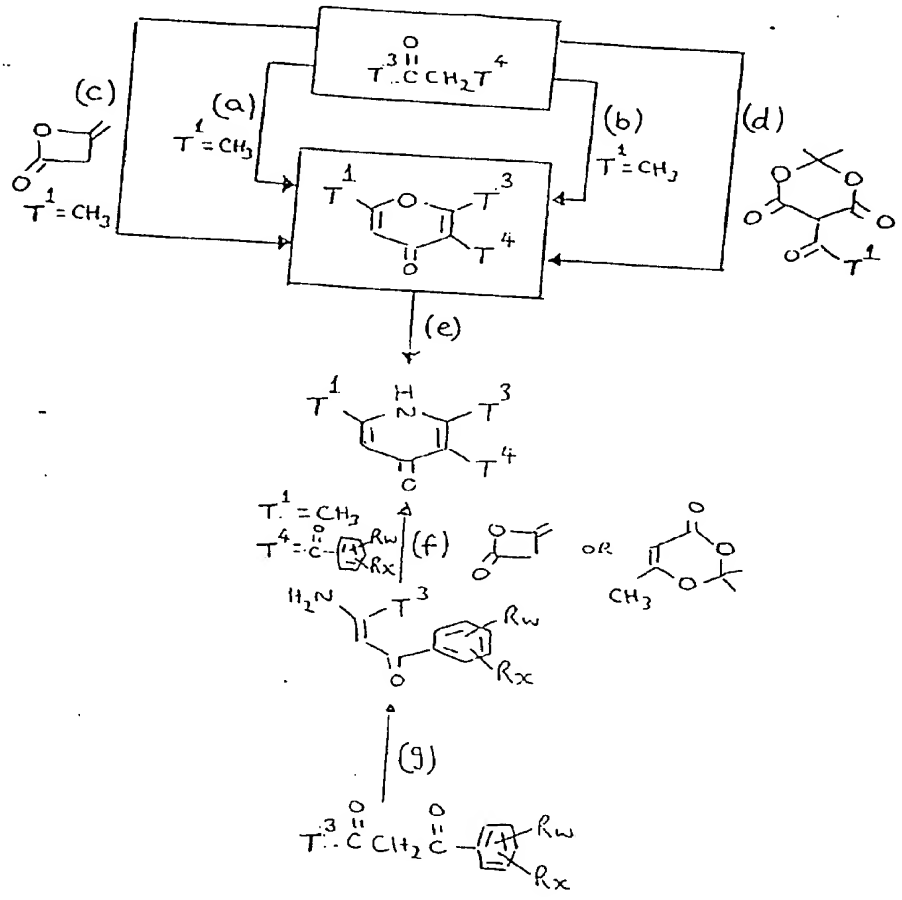
Note: Ph = phenyl
Reagents: (a) $POCl_3$/DMF
(b) Catalytic hydrogenation over palladium on carbon
(c) N-Chlorosuccinimide, dichloromethane
(d) (i) n-BuLi, THF/hexane, -78 to 0°C
(ii) $PhSO_2Cl$, THF, -78 to ambient
(e) NaI, aqueous HI, methyl ethyl ketone, reflux
(f) CuI, KF, triethyl(trifluoromethyl)silane, DMF/NMP, 80°C
(g) NaOH, aqu. methanol, reflux

Scheme 9



Note: R" = lower alkyl; Tos = p-toluenesulphonyl (tosyl)
Reagents: (a) Heat, 120°C
(b) p-Toluenesulphonyl isocyanate, acetonitrile, reflux
(c) Lithium aluminium hydride, THF, reflux
(d) Activated MnO_2, toluene, reflux
(e) NaH, DMF, $BrCH_2CO_2CH_3$, 0°C
(f) (i) $NaN(SiMe_3)_2$, THF, 0°C; (ii) Pyridine, $SOCl_2$, 0°C
(g) $NaN(SiMe_3)_2$, THF
(h) NaH, DMF, $BrCH_2CN$, 0°C

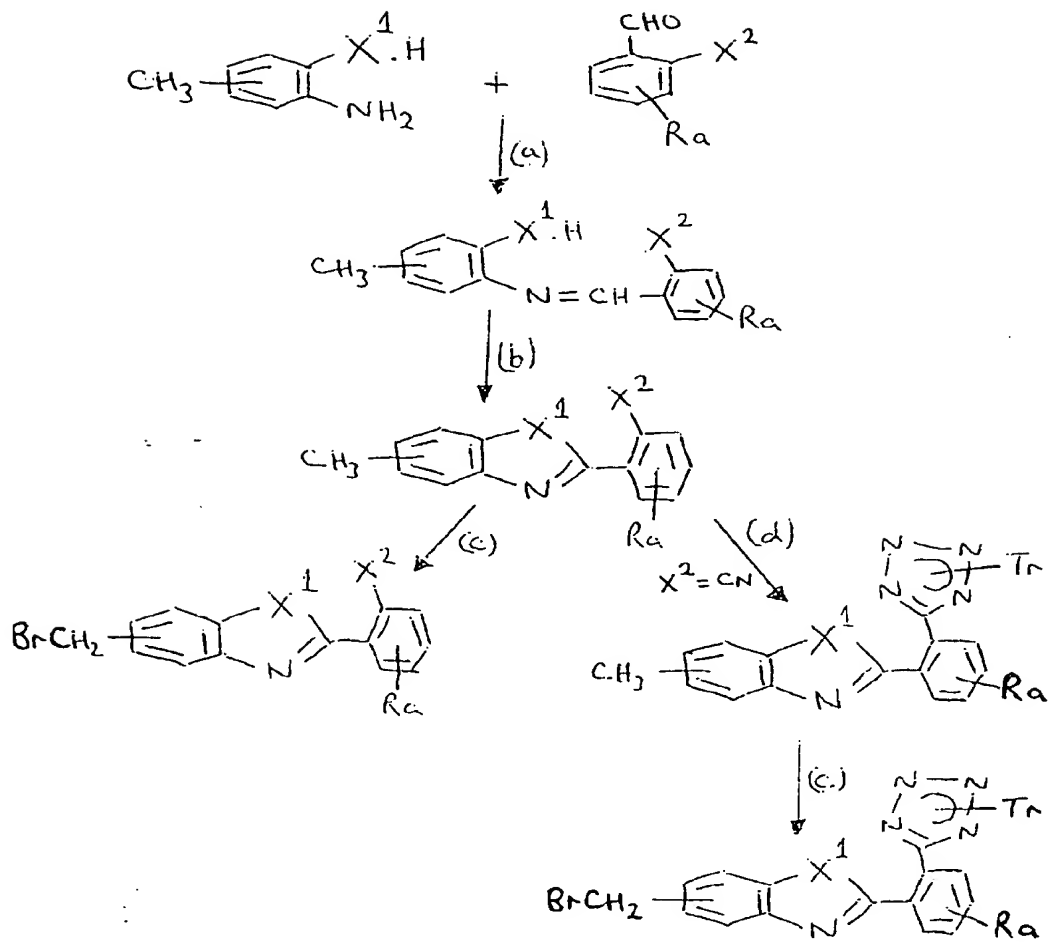
Scheme 10



Note: Rw and Rx are optional substituents

Reagents: (a) polyphosphoric acid, acetic acid
(b) (i) boron trifluoride, acetic anhydride
(ii) NaH or $(isopropyl)_2NLi$, ethyl acetate
(iii) benzene, PTSA, heat or conc. H_2SO_4, ambient temp.
(c) acetic acid, 0-50°C
(d) heat, 120°C
(e) ethanolic ammonia, 120°C, sealed tube
(f) heat
(g) ethanolic ammonia

Scheme 11



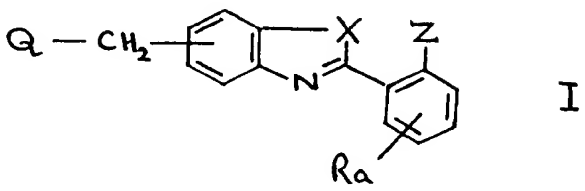
Note: X^1 = oxygen, sulphur or -NH-; X^2 = cyano, nitro or alkoxycarbonyl; Tr = triphenylmethyl (trityl)

Reagents: (a) ethanol, reflux
(b) Lead tetracetate, $CHCl_3$
(c) N-bromosuccinimide, azo(bisisobutyronitrile), CCl_4, reflux
(d) (i) $Bu_3Sn.N_3$/toluene; HCl/toluene
(ii) Tr.Cl/Et_3N/CH_2Cl_2

Claims

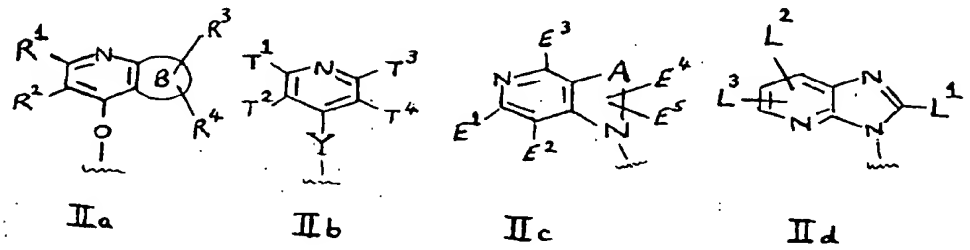
Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE

1. A heterocyclic derivative of the formula I



I

wherein Q is selected from a group of the partial structural formula IIa, IIb, IIc or IId



IIa IIb IIc IId

in which ring B of formula IIa completes a benzene or pyridine ring;
R^1 and T^1 are independently selected from (1-8C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-4C)alkyl, phenyl, phenyl(1-4C)alkyl or substituted (1-4C)alkyl, the latter containing one or more fluoro substituents or bearing an (1-4C)alkoxy substituent;
R^2 and T^2 are independently selected from hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, phenyl or phenyl(1-4C)alkyl;
R^3 and R^4 are optional substituents on ring B independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano, nitro, fluoro(1-4C)alkoxy, hydroxy or hydroxy(1-4C)alkyl;
T^3 is selected from halogeno, (1-4C)alkoxy, amino, alkylamino and dialkylamino of up to 6 carbon atoms and any of the values defined for T^1;
T^4 is selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkyl containing one or more fluoro substituents, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, halogeno, cyano, nitro, carbamoyl, (1-4C)alkanoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, amino, alkylamino and dialkylamino of up to 6 carbon atoms, and a group of the formula $-A^1.B^1$ wherein A^1 is (1-6C)alkylene, a carbonyl group or a direct bond and B^1 is

(1) an unsubstituted phenyl or phenyl bearing one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl, nitro, hydroxy, carboxy, (1-4C)alkanoylamino, (1-4C)alkanoyl, fluoro(1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, carbamoyl, N-alkyl or di-(N-alkyl)carbamoyl of up to 7 carbon atoms, sulphamoyl, N-alkyl or di-(N-alkyl)sulphamoyl of up to 6 carbon atoms, (1-4C)alkoxycarbonyl, (1-4C)alkanesulphonamido, (1-4C)alkyl.$S(O)_n$- [in which n is zero, 1 or 2] and 1H-tetrazol-5-yl; or B^1 is

(2) a 5 or 6-membered saturated or unsaturated heterocyclic ring optionally bearing a (1-4C)alkyl group and containing a single heteroatom selected from oxygen, sulphur and nitrogen or containing two heteroatoms one of which is nitrogen and the other is oxygen, sulphur or nitrogen;

or T^3 and T^4 together form an (3-6C)alkenylene group, an (3-6C)alkylene group or an (3-6C)alkylene group in which a methylene is replaced by carbonyl, provided that when T^3 and T^4 together form one of said latter three groups then T^2 is additionally selected from any of the previous values defined for T^4;

Y is oxygen or a group of the formula -NRb- wherein Rb is hydrogen, (1-4C)alkyl, (1-4C)alkanoyl or benzoyl;
linking group A of formula IIc is selected from -CH=CH-, -CH=CH-CO-, -CO-CH=CH-, -CO-CH_2-CH_2-, -CH_2-CH_2-CO, -CH_2-CO and -CO-CH_2-;
E^1 is hydrogen, (1-8C)alkyl or trifluoromethyl;
E^2 is hydrogen, (1-8C)alkyl, halogeno, (1-4C)alkoxy, trifluoromethyl, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, (1-4C)alkanoyl, (1-4C)alkyl.$S(O)_m$- [in which m is zero, 1 or 2] or phenylsulphonyl;
E^3 is hydrogen, (1-8C)alkyl, (1-4C)alkoxy, halogeno or trifluoromethyl;
E^4 and E^5 are optional substituents on linking group A independently selected from (1-4C)alkyl, substituted (1-4C)alkyl containing one or more fluoro substituents, phenyl, pyridyl, alkoxy, halogeno, cyano, nitro, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, carbamoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl and (1-4C)alkanoyl;
L^1 is (1-8C)alkyl;
L^2 and L^3 are independently selected from hydrogen and (1-4C)alkyl;
X is oxygen, sulphur or a group of the formula -NRc wherein Rc is hydrogen or (1-4C)alkyl;
Ra is selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro;
Z is 1H-tetrazol-5-yl, carboxy or a group of the formula CF_3SO_2NH-;
and wherein any of said phenyl moieties of R^1, R^2, T^1, T^2, T^3 or E^2 may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano and trifluoromethyl; or a non-toxic salt thereof.

2. A compound as claimed in claim 1 wherein R^1 and T^1 are independently selected from methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopentyl-ethyl, phenyl, benzyl, 1-phenylethyl, 2-phenylethyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 2-methoxyethyl and 2-ethoxyethyl;
R^2 and T^2 are independently selected from hydrogen, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopentyl-ethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl, 3-methyl-3-butenyloxycarbonyl, cyano, nitro, phenyl, benzyl, 1-phenylethyl and 2-phenylethyl;
R^3 and R^4 are optional substituents on ring B independently selected from methyl, ethyl, methoxy, ethoxy, chloro, bromo, iodo, trifluoromethyl, cyano, nitro, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 3,3,3-trifluoropropoxy, hydroxy, hydroxymethyl, 1-hydroxyethyl and 2-hydroxyethyl;
T^3 is selected from methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopentyl-ethyl, phenyl, benzyl, 1-phenylethyl, 2-phenylethyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 2-methoxyethyl, 2-ethoxyethyl, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, amino, methylamino, ethylamino, butylamino, dimethylamino, diethylamino and dipropylamino;
T^4 is selected from hydrogen, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl, 3-methyl-3-butenyloxycarbonyl, fluoro, chloro, bromo, iodo, cyano, nitro, carbamoyl, formyl, acetyl, butyryl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, amino, methylamino, ethylamino, butylamino, dimethylamino, diethylamino, dipropylamino, and a group of the formula **-A^1.B^1** wherein A^1 is methylene, ethylene, propylene, a carbonyl group or a direct bond and B^1 is
(1) an unsubstituted phenyl or phenyl bearing one or two substituents independently selected from methyl, ethyl, methoxy, ethoxy, chloro, bromo, iodo, cyano, trifluoromethyl, nitro, hydroxy, carboxy, formamido, acetamido, propanamido, formyl, acetyl, butyryl, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 3,3,3-trifluoropropoxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-methoxyethyl, 2-ethoxyethyl, carbamoyl, N-methylcarbamoyl and N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, sulphamoyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, methanesulphonamido, ethanesulphonamido, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl and 1H-tetrazol-5-yl; or B^1 is
(2) a heterocyclic ring selected from thienyl, furyl, pyrrolyl, pyrrolidinyl, pyridyl, piperidyl, imidazolyl, imidazolidinyl, pyrazolyl, pyrazolinyl, thiazolyl, thiazolinyl, oxazolyl, oxazolidinyl, pyrimidinyl, pyrazinyl,

pyridazinyl, piperazinyl, morpholinyl and thiomorpholinyl, said ring optionally bearing a methyl or ethyl group;
or T^3 and T^4 together form a trimethylene, tetramethylene, pentamethylene, 1-propenylene, 2-propenylene, 1-butenylene, 2-butenylene, 3-butenylene, 1-oxopropylidene, 3-oxopropylidene, 1-oxobutylidene or 4-oxobutylidene group, provided that when T^3 and T^4 together form one of said latter twelve groups then T^2 is additionally selected from any of the previous values defined for T^4;
Y is oxygen or a group of the formula -NRb- wherein Rb is hydrogen, methyl, ethyl, formyl, acetyl, propanoyl or benzoyl;
E^1 is hydrogen, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl or trifluoromethyl;
E^2 is hydrogen, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, trifluoromethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl, 3-methyl-3-butenyloxycarbonyl, cyano, nitro, formyl, acetyl, butyryl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl or phenylsulphonyl;
E^3 is hydrogen, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy or trifluoromethyl;
E^4 and E^5 are optional substituents on linking group A independently selected from methyl, ethyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl, pyridyl, methoxy, ethoxy, chloro, bromo, iodo, cyano, nitro, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl, 3-methyl-3-butenyloxycarbonyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, formyl, acetyl and butyryl;
L^1 is methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl or hexyl;
L^2 and L^3 are independently selected from hydrogen, methyl and ethyl;
X is oxygen, sulphur or a group of the formula -NRc wherein Rc is hydrogen, methyl or ethyl;
Ra is selected from hydrogen, methyl, ethyl, methoxy, ethoxy, chloro, bromo, iodo, trifluoromethyl, cyano and nitro; and wherein any of said phenyl moietiesof R^1, R^2, T^1, T^2, T^3 or E^2 may be unsubstituted or bear one or two substituents independently selected from methyl, ethyl, methoxy, ethoxy, chloro, bromo, iodo, cyano and trifluoromethyl; or a non-toxic salt thereof.

3. A compound as claimed in claim 1 or 2 but excluding those compounds wherein one or both of E^4 and E^5 is selected from phenyl, pyridyl, carbamoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or a non-toxic salt thereof.

4. A compound of the formula I as claimed in claim 1, 2 or 3 wherein Q is a group of partial structural formula IIa.

5. A compound of the formula I as claimed in claim 1, 2 or 3 wherein Q is a group of partial structural formula IIb.

6. A compound of the formula I as claimed in claim 1,2 or 3 wherein Q is a group of partial structural formula IIc.

7. A compound of the formula I as claimed in claim 1,2 or 3 wherein Q is a group of partial structural formula IId.

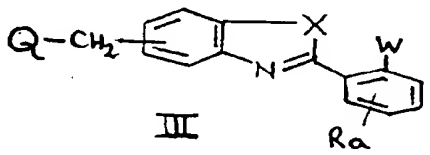
8. A compound of formula I as claimed in claim 1, 2 or 3 wherein Q is selected from
2-(1-4C)alkylquinolin-4-yloxy,
2-(1-4C)alkyl-5,6,7,8-tetrahydroquinolin-4-yloxy,
2,6-di-(1-4C)alkyl-3-halogenopyrid-4-ylamino,
2,6-di-(1-4C)alkyl-4-halogeno-1H-pyrrolo[3,2-c]pyrid-1-yl,
5,7-di-(1-4C)alkyl-2-oxo-1,2-dihydro-1,6-naphthyridin-1-yl,
5,7-di-(1-4C)alkyl-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-1-yl, 2-(1-4C)alkyl-3H-imidazo[4,5-b]pyrid-3-yl and
2,5,7-tri-(1-4C)alkyl-3H-imidazo[4,5-b]pyrid-3-yl.

9. A compound of the formula I as claimed in any preceding claim wherein X is oxygen.

10. A compound of the formula I selected from:-
2-ethyl-5,6,7,8-tetrahydro-4-[(2-(2-(1H-tetrazol-5-yl)phenyl)benzoxazol-5-yl)methoxy]quinoline and
5,7-dimethyl-2-propyl-3-[(2-(2-(1H-tetrazol-5-yl)phenyl)benzoxazol-5-yl)methyl]-3H-imidazo[4,5-b]pyridine;
or a non-toxic salt thereof.

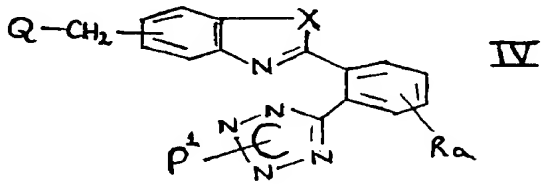
11. A salt as claimed in any one preceding claim which is selected from salts with acids forming physiologically acceptable anions and salts with bases forming physiologically acceptable cations.

12. A process for the manufacture of a compound of the formula I, or a non-toxic salt thereof, as claimed in claim 1, which is characterised in that:-
(a) For those compounds in which Z is carboxy, a carboxylic acid derivative of the formula III



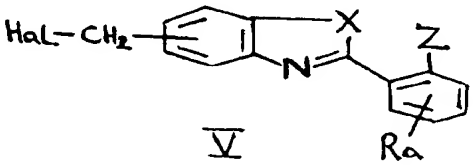
III

in which W is a protected carboxy group selected from (1-6C)alkoxycarbonyl, phenoxycarbonyl, benzyloxycarbonyl and carbamoyl, is converted to carboxy;
(b) For those compounds of the formula I wherein Z is tetrazolyl, a compound of the formula IV



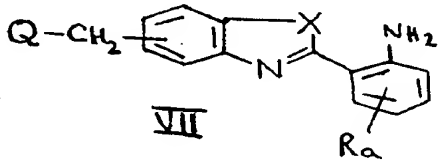
IV

in which P^1 is a protecting group affixed to the nitrogen of the tetrazolyl moiety, is deprotected;
(c) A compound of the formula **Q.H** is alkylated with a compound of the formula V



V

wherein **Hal.** stands for a suitable leaving group; or
(d) For those compounds of the formula I wherein Z is a group of the formula CF_3SO_2NH-, a compound of the formula VII



VII

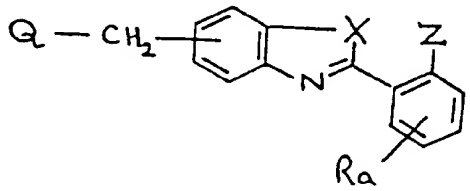
is reacted with trifluoromethanesulphonic anhydride;
whereafter when a compound of the formula I is required wherein Z is 1H-tetrazol-5-yl, a compound of the formula I wherein Z is carboxy is converted into the corresponding nitrile under standard conditions, followed by reaction of the nitrile with an azide;
whereafter, where necessary, any protecting group present is removed; whereafter when a non-toxic salt of a compound of the formula I is required, it is obtained by reaction with the appropriate acid or base affording a physiologically acceptable ion, or by any other salt formation procedure; and
when an optically active form of a compound of the formula I is required, one of the aforesaid processes (a)-(d) is carried out with an optically active starting material, or the racemic form of a compound of formula I is resolved by reaction with an optically active form of a suitable organic base followed by conventional separation of the of the diastereoisomeric mixture of salts thus obtained, and liberation of the required optically active form of said compound of formula I by conventional treatment with acid;
and wherein Q, X, Z and Ra have any of the meanings defined in any of claims 1 to 9 unless otherwise stated.

13. A pharmaceutical composition which comprises a compound of the formula I, or a non-toxic salt thereof, as claimed in any of claims 1 to 11, together with a pharmaceutically acceptable diluent or carrier.

Patentansprüche

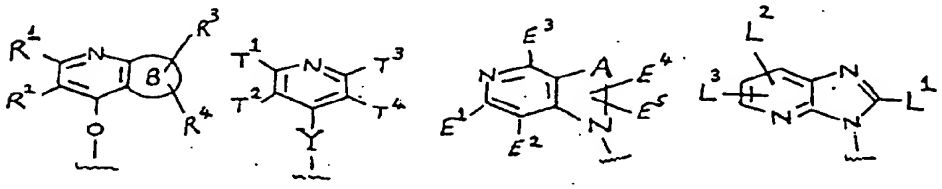
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE

1. Heterocyclisches Derivat der Formel (I)



(I)

worin Q gewählt ist aus einer Gruppe von Gruppen der Partial-Strukturformeln (IIa), (IIb), (IIc) oder (IId)



(IIa) (IIb) (IIc) (IId)

worin Ring B der Formel (IIa) einen Benzolring oder Pyridinring vervollständigt;
R^1 und T^1 unabhängig voneinander gewählt sind aus (C_1- bis C_8-)Alkyl, (C_3- bis C_8-)Cycloalkyl, (C_3- bis C_8)-Cycloalkyl-(C_1- bis C_4-)alkyl, Phenyl, Phenyl-(C_1- bis C_4-)alkyl oder substituiertes (C_1- bis C_4-)Alkyl, wobei die letztgenannte Gruppe einen oder mehrere Fluor-Substituenten enthält oder einen (C_1- bis C_4-)Alkoxy-Substituenten trägt;
R^2 und T^2 unabhängig voneinander gewählt sind aus Wasserstoff, (C_1- bis C_8-)Alkyl, (C_3-bis C_8-)Cycloalkyl, (C_3- bis C_8-)Cycloalkyl-(C_1- bis C_4-)alkyl, Carboxy, (C_1- bis C_4-)Alkoxycarbonyl, (C_3- bis C_6-)Alkenyloxycarbonyl, Cyano, Nitro, Phenyl oder Phenyl-(C_1- bis C_4)-alkyl;
R^3 und R^4 gegebenfalls vorhandene Substituenten an Ring B sind, die unabhängig voneinander gewählt

sind aus (C_1- bis C_4-)Alkyl, (C_1- bis C_4-)Alkoxy, Halogen, Trifluormethyl, Cyano, Nitro, Fluor-(C_1- bis C_4-)alkoxy, Hydroxy oder Hydroxy-(C_1- bis C_4-)alkyl;

T^3 gewählt ist aus Halogen, (C_1- bis C_4-)Alkoxy, Amino, Alkylamino und Dialkylamino mit bis zu 6 Kohlenstoffatomen und jeder der Bedeutungen, die für T^1 definiert sind;

T^4 gewählt ist aus Wasserstoff (C_1- bis C_4-)Alkyl, (C_1- bis C_4-)Alkoxy, (C_1- bis C_4-)Alkyl, das einen oder mehrere Fluor-Substituenten enthält, Carboxy, (C_1- bis C_4-)Alkoxycarbonyl, (C_3- bis C_6-)Alkenyloxycarbonyl, Halogen, Cyano, Nitro, Carbamoyl, (C_1- bis C_4-)Alkanoyl, N-Alkylcarbamoyl und Di-(N-alkyl-)carbamoyl mit bis zu 7 Kohlenstoffatomen, Amino, Alkylamino und Dialkylamino mit bis zu 6 Kohlenstoffatomen und einer Gruppe der Formel -A^1.B^1, worin A^1 für eine (C_1- bis C_6-)Alkylengruppe, eine Carbonylgruppe oder eine direkte Bindung steht und B^1 steht für

(1) eine unsubstituierte Phenylgruppe oder eine Phenylgruppe, die einen oder zwei Substituenten trägt, die unabhängig voneinander gewählt sind aus (C_1- bis C_4-)Alkyl, (C_1- bis C_4-)Alkoxy, Halogen, Cyano, Trifluormethyl, Nitro, Hydroxy, Carboxy, (C_1- bis C_4-)Alkanoylamino, (C_1- bis C_4-)Alkanoyl, Fluor-(C_1- bis C_4-)alkoxy, Hydroxy-(C_1- bis C_4-)alkyl, (C_1- bis C_4-)Alkoxy-(C_1- bis C_4-)alkyl, Carbamoyl, N-Alkyl- oder Di-(N-Alkyl-)carbamoyl mit bis zu 7 Kohlenstoffatomen, Sulfamoyl, N-Alkyl oder Di-(N-Alkyl-)sulfamoyl mit bis zu 6 Kohlenstoffatomen, (C_1- bis C_4-)Alkoxycarbonyl, (C_1- bis C_4-)Alkansulfonamido, (C_1- bis C_4-)Alkyl.$S(O)_n$- [worin n für 0, 1 oder 2 steht] und 1H-Tetrazol-5-yl; oder B^1 steht für

(2) einen fünf- oder sechsgliedrigen gesättigten oder ungesättigten heterocyclischen Ring, der gegebenenfalls eine (C_1- bis C_4-)Alkylgruppe trägt und ein einziges Heteroatom enthält, das aus Sauerstoff, Schwefel und Stickstoff gewählt ist, oder zwei Heteroatome enthält, von denen eines Stickstoff ist und das andere Sauerstoff, Schwefel oder Stickstoff ist; oder

T^3 und T^4 zusammen eine (C_3- bis C_6-)Alkenylengruppe, eine (C_3- bis C_6-)Alkylengruppe oder eine (C_3- bis C_6-)Alkylengruppe bilden, in der ein Methylenrest durch einen Carbonylrest ersetzt ist, mit der Maßgabe, daß dann, wenn T^3 und T^4 zusammen eine der letztgenannten drei Gruppen bilden, T^2 außerdem gewählt ist aus irgendeiner der vorstehend für T^4 angegebenen Bedeutungen;

Y für Sauerstoff oder eine Gruppe der Formel -NRb- steht, worin Rb für Wasserstoff, (C_1-bis C_4-)Alkyl, (C_1- bis C_4-)Alkanoyl oder Benzoyl steht;

die Verbindungsgruppe A in Formel (IIc) gewählt ist aus -CH=CH-, -CH=CH-CO-, -CO-CH=CH-, -CO-CH_2-CH_2-, -CH_2-CH_2-CO-, -CH_2-CO- und -CO-CH_2-;

E^1 für Wasserstoff, (C_1- bis C_8-)Alkyl oder Trifluormethyl steht;

E^2 für Wasserstoff, (C_1- bis C_8-)Alkyl, Halogen, (C_1- bis C_4-)Alkoxy, Trifluormethyl, Carboxy, (C_1- bis C_4-)Alkoxycarbonyl, (C_3- bis C_6-)Alkenyloxycarbonyl, Cyano, Nitro, (C_1-bis C_4-)Alkanoyl, (C_1- bis C_4-)Alkyl.$S(O)_m$- [worin m für 0, 1 oder 2 steht] oder Phenylsulfonyl steht;

E^3 für Wasserstoff, (C_1- bis C_8-)Alkyl, (C_1- bis C_4-)Alkoxy, Halogen oder Trifluormethyl steht;

E^4 und E^5 gegebenenfalls vorhandene Substituenten an der Verbindungsgruppe A sind, die unabhängig voneinander gewählt sind aus (C_1- bis C_4-)Alkyl, substituiertes (C_1- bis C_4)-Alkyl, das einen oder mehrere Fluor-Substituenten enthält, Phenyl, Pyridyl, Alkoxy, Halogen, Cyano, Nitro, Carboxy, (C_1- bis C_4-)Alkoxycarbonyl, (C_3- bis C_6-)Alkenyloxycarbonyl, Carbamoyl, N-Alkylcarbamoyl und Di-(N-alkyl-)carbamoyl mit bis zu 7 Kohlenstoffatomen, (C_1- bis C_4-)Alkylthio, (C_1- bis C_4-)Alkylsulfinyl, (C_1- bis C_4)-Alkylsulfonyl, Phenylthio, Phenylsulfinyl, Phenylsulfonyl und (C_1- bis C_4-)Alkanoyl;

L^1 für (C_1- bis C_8-)Alkyl steht;

L^2 und L^3 unabhängig voneinander gewählt sind aus Wasserstoff und (C_1- bis C_4-)Alkyl;

X für Sauerstoff, Schwefel oder eine Gruppe der Formel -NRc- steht, worin Rc für Wasserstoff oder (C_1- bis C_4-)Alkyl steht;

Ra gewählt ist aus Wasserstoff, (C_1- bis C_4-)Alkyl, (C_1- bis C_4-)Alkoxy, Halogen, Trifluormethyl, Cyano und Nitro; und

Z für 1H-Tetrazol-5-yl, Carboxy oder eine Gruppe der Formel CF_3SO_2NH- steht;

und worin jede der Phenyleinheiten bei den Resten R^1, R^2, T^1, T^2, T^3 oder E^2 unsubstituiert sein kann oder einen oder zwei Substituenten tragen kann, die unabhängig voneinander gewählt sind aus (C_1- bis C_4-)Alkyl, (C_1- bis C_4-)Alkoxy, Halogen, Cyano und Trifluormethyl;

oder ein nicht toxisches Salz einer derartigen Verbindung.

2. Verbindung nach Anspruch 1, worin

R^1 und T^1 unabhängig voneinander gewählt sind aus Methyl, Ethyl, Propyl, Butyl, Isobutyl, sec-Butyl, Pentyl, Hexyl, Cyclopropyl, Cyclopentyl, Cyclohexyl, Cyclopropylmethyl, Cyclopentylmethyl, Cyclohexylmethyl, 2-Cyclopentylethyl, Phenyl, Benzyl, 1-Phenylethyl, 2-Phenylethyl, Fluormethyl, Trifluormethyl, 2,2,2-Trifluorethyl, Pentafluorethyl, 2-Methoxyethyl und 2-Ethoxyethyl;

R^2 und T^2 unabhängig voneinander gewählt sind aus Wasserstoff, Methyl, Ethyl, Propyl, Butyl, Isobutyl,

sec-Butyl, Pentyl, Hexyl, Cyclopropyl, Cyclopentyl, Cyclohexyl, Cyclopropylmethyl, Cyclopentylmethyl, Cyclohexylmethyl, 2-Cyclopentylethyl, Carboxy, Methoxycarbonyl, Ethoxycarbonyl, Propoxycarbonyl, Allyloxycarbonyl, 2-Methyl-2-propenyloxycarbonyl, 3-Methyl-3-butenyloxycarbonyl, Cyano, Nitro, Phenyl, Benzyl, 1-Phenylethyl und 2-Phenylethyl;

R^3 und R^4 gegebenenfalls vorhandene Substituenten am Ring B sind, die unabhängig voneinander gewählt sind aus Methyl, Ethyl, Methoxy, Ethoxy, Chlor, Brom, Iod, Trifluormethyl, Cyano, Nitro, Trifluormethoxy, 2-Fluorethoxy, 2,2,2-Trifluorethoxy, 3,3,3-Trifluorpropoxy, Hydroxy, Hydroxymethyl, 1-Hydroxyethyl und 2-Hydroxyethyl;

T^3 gewählt ist aus Methyl, Ethyl, Propyl, Butyl, Isobutyl, sec-Butyl, Pentyl, Hexyl, Cyclopropyl, Cyclopentyl, Cyclohexyl, Cyclopropylmethyl, Cyclopentylmethyl, Cyclohexylmethyl, 2-Cyclopentylethyl, Phenyl, Benzyl, 1-Phenylethyl, 2-Phenylethyl, Fluormethyl, Trifluormethyl, 2,2,2-Trifluorethyl, Pentafluorethyl, 2-Methoxyethyl, 2-Ethoxyethyl, Fluor, Chlor, Brom, Iod, Methoxy, Ethoxy, Propoxy, Amino, Methylamino, Ethylamino, Butylamino, Dimethylamino, Diethylamino und Dipropylamino;

T^4 gewählt ist aus Wasserstoff, Methyl, Ethyl, Propyl, Methoxy, Ethoxy, Propoxy, Fluormethyl, Trifluormethyl, 2,2,2-Trifluorethyl, Pentafluorethyl, Carboxy, Methoxycarbonyl, Ethoxycarbonyl, Propoxycarbonyl, Allyloxycarbonyl, 2-Methyl-2-propenyloxycarbonyl, 3-Methyl-3-butenyloxycarbonyl, Fluor, Chlor, Brom, Iod, Cyano, Nitro, Carbamoyl, Formyl, Acetyl, Butyryl, N-Methylcarbamoyl, N-Ethylcarbamoyl, N,N-Dimethylcarbamoyl, N,N-Diethylcarbamoyl, Amino, Methylamino, Ethylamino, Butylamino, Dimethylamino, Diethylamino, Dipropylamino, und eine Gruppe der Formel $-A^1.B^1$, worin A^1 für Methylen, Ethylen, Propylen, eine Carbonylgruppe oder eine direkte Bindung steht und B^1 steht für

(1) unsubstituiertes Phenyl oder Phenyl, das einen oder zwei Substituenten trägt, die unabhängig voneinander gewählt sind aus Methyl, Ethyl, Methoxy, Ethoxy, Chlor, Brom, Iod, Cyano, Trifluormethyl, Nitro, Hydroxy, Carboxy, Formamido, Acetamido, Propanamido, Formyl, Acetyl, Butyryl, Trifluormethoxy, 2-Fluorethoxy, 2,2,2-Trifluorethoxy, 3,3,3-Trifluorpropoxy, Hydroxymethyl, 1-Hydroxyethyl, 2-Hydroxyethyl, 2-Methoxyethyl, 2-Ethoxyethyl, Carbamoyl, N-Methylcarbamoyl, N-Ethylcarbamoyl, N,N-Dimethylcarbamoyl, N,N-Diethylcarbamoyl, Sulfamoyl, N-Methylsulfamoyl, N-Ethylsulfamoyl, N,N-Dimethylsulfamoyl, N,N-Diethylsulfamoyl, Methoxycarbonyl, Ethoxycarbonyl, Propoxycarbonyl, Methansulfonamido, Ethansulfonamido, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Methylsulfonyl, Ethylsulfonyl und 1H-Tetrazol-5-yl; oder B^1 steht für

(2) einen heterocyclischen Ring, der gewählt ist aus Thienyl, Furyl, Pyrrolyl, Pyrrolidinyl, Pyridyl, Piperidyl, Imidazolyl, Imidazolidinyl, Pyrazolyl, Pyrazolinyl, Thiazolyl, Thiazolinyl, Oxazolyl, Oxazolidinyl, Pyrimidinyl, Pyrazinyl, Pyridazinyl, Piperazinyl, Morpholinyl und Thiomorpholinyl, wobei der Ring gegebenenfalls eine Methyl- oder Ethylgruppe trägt;

oder T^3 und T^4 zusammen eine Trimethylen-Gruppe, Tetramethylen-Gruppe, Pentamethylen-Gruppe, 1-Propenylen-Gruppe, 2-Propenylen-Gruppe, 1-Butenylen-Gruppe, 2-Butenylen-Gruppe, 3-Butenylen-Gruppe, 1-Oxopropyliden-Gruppe, 3-Oxypropyliden-Gruppe, 1-Oxobutyliden-Gruppe oder 4-Oxobutyliden-Gruppe bilden, mit der Maßgabe, daß dann, wenn T^3 und T^4 zusammen eine der letztgenannten zwölf Gruppen bilden, T^2 außerdem gewählt ist aus einer der vorstehend für T^4 definierten Bedeutungen;

Y für Sauerstoff oder eine Gruppe der Formel -NRb- steht, worin Rb für Wasserstoff, Methyl, Ethyl, Formyl, Acetyl, Propanoyl oder Benzoyl steht;

E^1 für Wasserstoff, Methyl, Ethyl, Propyl, Butyl, Isobutyl, sec-Butyl, Pentyl, Hexyl oder Trifluormethyl steht;

E^2 für Wasserstoff, Methyl, Ethyl, Propyl, Butyl, Isobutyl, sec-Butyl, Pentyl, Hexyl, Fluor, Chlor, Brom, Iod, Methoxy, Ethoxy, Propoxy, Trifluormethyl, Carboxy, Methoxycarbonyl, Ethoxycarbonyl, Propoxycarbonyl, Allyloxycarbonyl, 2-Methyl-2-propenyloxycarbonyl, 3-Methyl-3-butenyloxycarbonyl, Cyano, Nitro, Formyl, Acetyl, Butyryl, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Methylsulfonyl, Ethylsulfonyl oder Phenylsulfonyl steht;

E^3 für Wasserstoff, Methyl, Ethyl, Propyl, Butyl, Isobutyl, sec-Butyl, Pentyl, Hexyl, Fluor, Chlor, Brom, Iod, Methoxy, Ethoxy, Propoxy oder Trifluormethyl steht;

E^4 und E^5 gegebenenfalls vorhandene Substituenten an der Verbindungsgruppe A sind, die unabhängig voneinander gewählt sind aus Methyl, Ethyl, Fluormethyl, Trifluormethyl, 2,2,2-Trifluorethyl, Pentafluorethyl, Phenyl, Pyridyl, Methoxy, Ethoxy, Chlor, Brom, Iod, Cyano, Nitro, Carboxy, Methoxycarbonyl, Ethoxycarbonyl, Propoxycarbonyl, Allyloxycarbonyl ,2-Methyl-2-propenyloxycarbonyl, 3-Methyl-3-butenyloxycarbonyl,Carbamoyl, N-Methylcarbamoyl, N-Ethylcarbamoyl, N,N-Dimethylcarbamoyl, N,N-Diethylcarbamoyl, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Methylsulfonyl, Ethylsulfonyl, Phenylthio, Phenylsulfinyl, Phenylsulfonyl, Formyl, Acetyl und Butyryl;

L^1 für Methyl, Ethyl, Propyl, Butyl, Isobutyl, sec-Butyl, Pentyl oder Hexyl steht;

L^2 und L^3 unabhängig voneinander gewählt sind aus Wasserstoff, Methyl und Ethyl;
X für Sauerstoff, Schwefel oder eine Gruppe der Formel -NRc- steht, worin Rc für Wasserstoff, Methyl oder Ethyl steht;
Ra gewählt ist aus Wasserstoff, Methyl, Ethyl, Methoxy, Ethoxy, Chlor, Brom, Iod, Trifluormethyl, Cyano und Nitro; und
worin jede der Phenyleinheiten der Reste R^1, R^2, T^1, T^2, T^3 oder E^2 unsubstituiert sein kann oder einen oder zwei Substituenten tragen kann, die unabhängig voneinander gewählt sind aus Methyl, Ethyl, Methoxy, Ethoxy, Chlor, Brom, Iod, Cyano und Trifluormethyl;
oder ein nicht toxisches Salz einer derartigen Verbindung.

3. Verbindung nach Anspruch 1 oder 2, jedoch unter Ausschluß der Verbindungen, in denen einer oder beide der Reste E^4 und E^5 gewählt ist/sind aus Phenyl, Pyridyl, Carbamoyl, N-Alkylcarbamoyl und Di-(N-alkyl-)carbamoyl mit bis zu 7 Kohlenstoffatomen, (C_1- bis C_4)-Alkylthio, (C_1- bis C_4-)Alkylsulfinyl, (C_1- bis C_4-)Alkylsulfonyl, Phenylthio, Phenylsulfinyl und Phenylsulfonyl; oder ein nicht toxisches Salz einer derartigen Verbindung.

4. Verbindung der Formel (I) nach Anspruch 1, 2 oder 3, worin Q eine Gruppe der Partial-Strukturformel (IIa) ist.

5. Verbindung der Formel (I) nach Anspruch 1, 2 oder 3, worin Q eine Gruppe der Partial-Strukturformel (IIb) ist.

6. Verbindung der Formel (I) nach Anspruch 1, 2 oder 3, worin Q eine Gruppe der Partial-Strukturformel (IIc) ist.

7. Verbindung der Formel (I) nach Anspruch 1, 2 oder 3, worin Q eine Gruppe der Partial-Strukturformel (IId) ist.

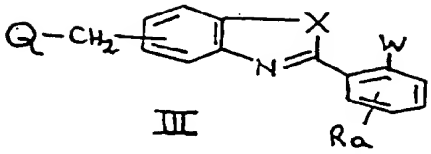
8. Verbindung der Formel (I) nach Anspruch 1, 2 oder 3, worin Q gewählt ist aus
2-(C_1- bis C_4-)Alkylchinolin-4-yloxy,
2-(C_1- bis C_4-)Alkyl-5,6,7,8-tetrahydrochinolin-4-yloxy,
2,6-Di-(C_1- bis C_4-)alkyl-3-halogenpyrid-4-ylamino,
2,6-Di-(C_1- bis C_4-)alkyl-4-halogen- 1H-pyrrol[3,2-c]pyrid-1-yl,
5,7-Di-(C_1- bis C_4-)alkyl-2-oxo-1,2-dihydro-1,6-naphthyridin-1-yl,
5,7-Di-(C_1- bis C_4-)alkyl-2-oxo- 1,2,3 4-tetrahydro-1,6-naphthyridin-1-yl,
2-(C_1- bis C_4-)Alkyl-3H-imidazo[4,5-b]pyrid-3-yl,
2,5,7-Tri-(C_1- bis C_4-)alkyl-3H-imidazo[4,5-b]pyrid-3-yl.

9. Verbindung der Formel (I) nach einem der vorangehenden Ansprüche, worin X Sauerstoff ist.

10. Verbindung der Formel (I), gewählt aus
2-Ethyl-5,6,7,8-tetrahydro-4-[(2-(1H-tetrazol-5-yl-)phenyl-)benzoxazol-5-yl-)methoxy]chinolin, und
5,7-Dimethyl-2-propyl-3-[(2-(2-(1H-tetrazol-5-yl-)phenyl-)benzoxazol-5-yl-)methyl-]-3H-imidazo[4,5-b]pyridin; oder ein nicht toxisches Salz davon.

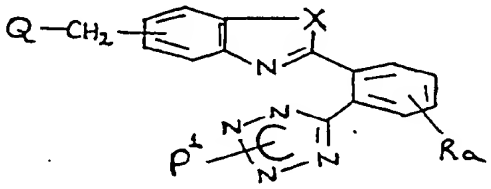
11. Salz nach einem der vorangehenden Ansprüche, das gewählt ist aus Salzen mit Säuren, die physiologisch annehmbare Anionen bilden, und Salzen mit Basen, die physiologisch annehmbare Kationen bilden.

12. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines nichttoxischen Salzes davon nach Anspruch 1, dadurch gekennzeichnet, daß
(a) zur Herstellung der Verbindungen, in denen Z für Carboxy steht, ein Carbonsäure-Derivat der Formel (III)



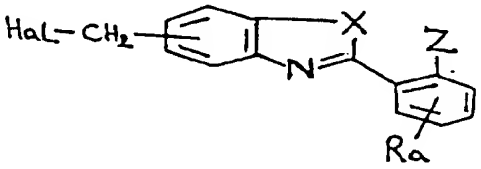
(III)

in der W eine geschützte Carboxy-Gruppe ist, die gewählt ist aus (C_1- bis C_6)-Alkoxycarbonyl, Phenoxycarbonyl, Benzyloxycarbonyl und Carbamoyl, in eine Carboxy-Gruppe umgewandelt wird;
(b) im Fall der Herstellung der Verbindungen der Formel (I), in der Z für Tetrazolyl steht, eine Verbindung der Formel (IV)



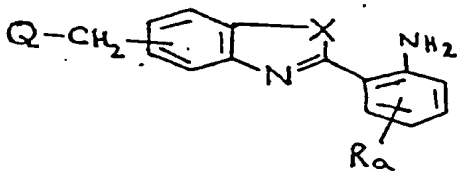
(IV)

worin P^1 für eine Schutzgruppe steht, die an das Stickstoffatom der Tetrazolyl-Einheit fixiert ist, von der Schutzgruppe befreit wird;
(c) eine Verbindung der Formel Q.H mit einer Verbindung der Formel (V)



(V)

worin Hal. für eine geeignete Abgangsgruppe steht, alkyliert wird; oder
(d) zur Herstellung der Verbindungen der Formel (I), worin Z eine Gruppe der Formel CF_3SO_2NH- ist, eine Verbindung der Formel (VII)



(VII)

mit Trifluormethansulfonsäureanhydrid umgesetzt wird;
wonach dann, wenn eine Verbindung der Formel (I) benötigt wird, worin Z für 1H-Tetrazol-5-yl steht, eine Verbindung der Formel (I), worin Z für Carboxy steht, in das entsprechende Nitril unter Standardbedingungen umgewandelt wird und dem eine Umsetzung des Nitrils mit einem Azid folgt, wonach dann, wenn dies erforderlich ist, irgendwelche Schutzgruppen, die im Molekül vorhanden sind, entfernt werden, wonach dann, wenn ein nichttoxisches Salz einer Verbindung der Formel (I) benötigt wird, dieses erhalten wird durch Umsetzung mit der geeigneten Säure oder Base unter Bereitstellung eines physiologisch annehmbaren Ions, oder durch irgendein anderes Verfahren zur Salzbildung; und

dann, wenn eine optisch aktive Form einer Verbindung der Formel (I) benötigt wird, einer der vorstehend genannten Verfahrensschritte (a) bis (d) mit einem optisch aktiven Ausgangsmaterial durchgeführt wird, oder die racemische Form einer Verbindung der Formel (I) durch Umsetzung mit einer optisch aktiven

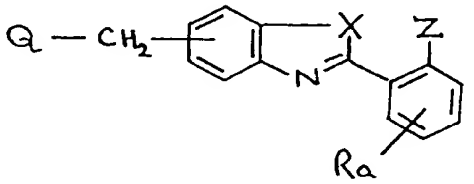
Form einer geeigneten organischen Base gelöst wird, gefolgt von einer herkömmlichen Trennung der Diastereoisomeren-Mischung der so erhaltenen Salze und Freisetzen der benötigten optisch aktiven Form der Verbindung der Formel (I) durch herkömmliche Behandlung mit Säure; und worin Q, X, Z und Ra irgendeine der Bedeutungen haben, wie sie in einem der Ansprüche 1 bis 9 definiert ist, solange nichts anderes angegeben ist.

13. Pharmazeutische Zubereitung, die eine Verbindung der Formel (I) oder ein nichttoxisches Salz davon nach einem der Ansprüche 1 bis 11 zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger umfaßt.

Revendications

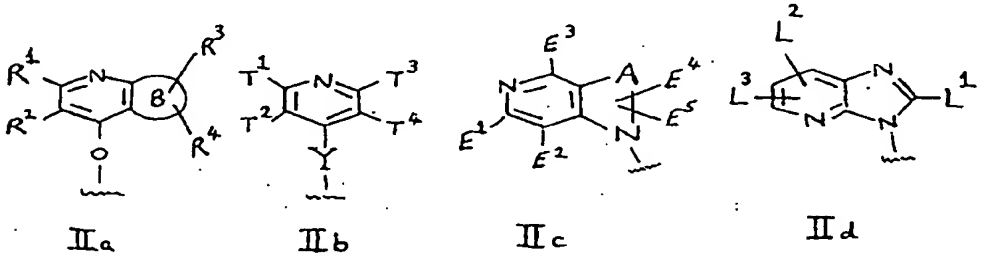
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NC, NL, PT, SE

1. Dérivé hétérocyclique de formule I



I

dans laquelle Q consiste en un groupe répondant à la formule structurale partielle IIa, IIb, IIc ou IId



IIa IIb IIc IId

dans laquelle le noyau B de la formule IIa complète un noyau benzénique ou pyridine ;

R^1 et T^1 sont choisis indépendamment entre des groupes alkyle en C_1 à C_8, cycloalkyle en C_3 à C_8, (cycloalkyle en C_3 à C_8)-(alkyle en C_1 à C_4), phényle, phényl(alkyle en C_1 à C_4) et alkyle en C_1 à C_4 substitué, ce dernier contenant un ou plusieurs substituants fluoro et portant un substituant alkoxy en C_1 à C_4 ;

R^2 et T^2 sont choisis indépendamment entre l'hydrogène et des groupes alkyle en C_1 à C_8, cycloalkyle en C_3 à C_8, (cycloalkyle en C_3 à C_8)-(alkyle en C_1 à C_4), carboxy, (alkoxy en C_1 à C_4)-carbonyle, (alcényle en C_3 à C_6)oxycarbonyle, cyano, nitro, phényle et phényl-(alkyle en C_1 à C_4) ;

R^3 et R^4 représentent des substituants facultatifs sur le noyau B choisis indépendamment entre des groupes alkyle en C_1 à C_4, alkoxy en C_1 à C_4, halogéno, trifluorométhyle, cyano, nitro, fluoralkoxy en C_1 à C_4, hydroxy et hydroxy-(alkyle en C_1 à C_4) ;

T^3 est choisi entre des groupes halogéno, alkoxy en C_1 à C_4, amino, alkylamino et dialkylamino ayant jusqu'à 6 atomes de carbone ainsi que n'importe lesquelles des valeurs définies pour T^1 ;

T^4 est choisi entre l'hydrogène et des groupes alkyle en C_1 à C_4, alkoxy en C_1 à C_4, alkyle en C_1 à C_4 contenant un ou plusieurs substituants fluoro, carboxy, (alkoxy en C_1 à C_4)-carbonyle, (alcényle en C_3 à C_6)-oxycarbonyle, halogéno, cyano, nitro, carbamoyle, alcanoyle en C_1 à C_4, N-alkylcarbamoyle et di(N-alkyl)carbamoyle ayant jusqu'à 7 atomes de carbone, amino, alkylamino et dialkylamino ayant jusqu'à 6 atomes de carbone, et un groupe de formule $-A^1.B^1$ dans laquelle A^1 représente un groupe alkylène

en C_1 à C_6, un groupe carbonyle ou une liaison directe et B^1 représente

(1) un groupe phényle non substitué ou phényle portant un ou deux substituants choisis indépendamment entre des groupes alkyle en C_1 à C_4, alkoxy en C_1 à C_4, halogéno, cyano, trifluorométhyle, nitro, hydroxy, carboxy, alcanoylamino en C_1 à C_4, alcanoyle en C_1 à C_4, fluoralkoxy en C_1 à C_4, hydroxyalkyle en C_1 à C_4, (alkoxy en C_1 à C_4)-(alkyle en C_1 à C_4), carbamoyle, N-alkyl- ou di-(N-alkyl)-carbamoyle ayant jusqu'à 7 atomes de carbone, sulfamoyle, N-alkyl- ou di-(N-alkyl)-sulfamoyle ayant jusqu'à 6 atomes de carbone, (alkoxy en C_1 à C_4)-carbonyle, alcanesulfonamido en C_1 à C_4, (alkyle en C_1 à C_4).$S(O)_n$- [dans lequel n est égal à zéro, 1 ou 2] et 1H-tétrazole-5-yle ; ou B^1 représente

(2) un noyau hétérocyclique saturé ou insaturé penta- ou hexagonal portant facultativement un groupe alkyle en C_1 à C_4 et contenant un seul hétéro-atome choisi entre l'oxygène, le soufre et l'azote, ou bien contenant deux hétéro-atomes dont l'un est l'azote et l'autre est l'oxygène, le soufre ou l'azote ;

ou bien T^3 et T^4 forment conjointement un groupe alcénylène en C_3 à C_6, un groupe alkylène en C_3 à C_6 ou un groupe alkylène en C_3 à C_6 dans lequel un groupe méthylène est remplacé par un groupe carbonyle, sous réserve que, lorsque T^3 et T^4 forment conjointement l'un de ces trois derniers groupes, T^2 soit choisi en outre entre n'importe lesquelles des valeurs définies précédemment pour T^4 ;

Y représente l'oxygène ou un groupe de formule -NRb- dans laquelle Rb représente l'hydrogène, un groupe alkyle en C_1 à C_4 alcanoyle en C_1 à C_4 ou benzoyle ;

le groupe de jonction A de la formule IIc est choisi entre les groupes -CH=CH-, -CH=CH-CO-, -CO-CH=CH-, -CO-CH_2-CH_2-, -CH_2-CH_2-CO, -CH_2-CO et -CO-CH_2- ;

E^1 représente l'hydrogène, un groupe alkyle en C_1 à C_8 ou trifluorométhyle ;

E^2 représente l'hydrogène, un groupe alkyle en C_1 à C_8, halogéno, alkoxy en C_1 à C_4, trifluorométhyle, carboxy, (alkoxy en C_1 à C_4)-carbonyle, (alcényle en C_3 à C_6)oxycarbonyle, cyano, nitro, alcanoyle en C_1 à C_4, (alkyle en C_1 à C_4).$S(O)_m$- [dans lequel m est égal à zéro, 1 ou 2] ou phénylsulfonyle ;

E^3 représente l'hydrogène, un groupe alkyle en C_1 à C_8, alkoxy en C_1 à C_4, halogéno ou trifluorométhyle ;

E^4 et E^5 représentent des substituants facultatifs sur le groupe de jonction A choisis indépendamment entre des groupes alkyle en C_1 à C_4, alkyle en C_1 à C_4 substitué contenant un ou plusieurs substituants fluoro, phényle, pyridyle, alkoxy, halogéno, cyano, nitro, carboxy, (alkoxy en C_1 à C_4)-carbonyle, (alcényle en C_3 à C_6)oxycarbonyle, carbamoyle, N-alkylcarbamoyle et di-(N-alkyl)carbamoyle ayant jusqu'à 7 atomes de carbone, alkylthio en C_1 à C_4, alkylsulfinyle en C_1 à C_4, alkylsulfonyle en C_1 à C_4, phénylthio, phénylsulfinyle, phénylsulfonyle et alcanoyle en C_1 à C_4 ;

L^1 représente un groupe alkyle en C_1 à C_8 ;

L^2 et L^3 sont choisis indépendamment entre l'hydrogène et un groupe alkyle en C_1 à C_4 ;

X représente l'oxygène, le soufre ou un groupe de formule -NRc dans laquelle Rc représente l'hydrogène ou un groupe alkyle en C_1 à C_4 ;

Ra est choisi entre l'hydrogène et des groupes alkyle en C_1 à C_4, alkoxy en C_1 à C_4, halogéno, trifluorométhyle, cyano et nitro ;

Z représente un groupe 1H-tétrazole-5-yle, carboxy ou un groupe de formule CF_3SO_2NH- ;

et dans laquelle n'importe lequel desdits groupements phényle de R^1, R^2, T^1, T^2, T^3 ou E^2 peut être non substitué ou peut porter un ou deux substituants choisis indépendamment entre des groupes alkyle en C_1 à C_4, alkoxy en C_1 à C_4, halogéno, cyano et trifluorométhyle ; ou un de ses sels non toxiques.

2. Composé suivant la revendication 1, dans lequel R^1 et T^1 sont choisis indépendamment entre les groupes méthyle, éthyle, propyle, butyle, isobutyle, sec-butyle, pentyle, hexyle, cyclopropyle, cyclopentyle, cyclohexyle, cyclopropylméthyle, cyclopentylméthyle, cyclohexylméthyle, 2-cyclopentyléthyle, phényle, benzyle, 1-phényléthyle, 2-phényléthyle, fluorométhyle, trifluorométhyle, 2,2,2-trifluoroéthyle, pentafluoréthyle, 2-méthoxyéthyle et 2-éthoxyéthyle ;

R^2 et T^2 sont choisis indépendamment entre l'hydrogène et les groupes méthyle, éthyle, propyle, butyle, isobutyle, sec-butyle, pentyle, hexyle, cyclopropyle, cyclopentyle, cyclohexyle, cyclopropylméthyle, cyclopentylméthyle, cyclohexylméthyle, 2-cyclopentyléthyle, carboxy, méthoxycarbonyle, éthoxycarbonyle, propoxycarbonyle, allyloxycarbonyle, 2-méthyl-2-propényloxycarbonyle, 3-méthyl-3-buténylcarbonyle, cyano, nitro, phényle, benzyle, 1-phényléthyle et 2-phényléthyle ;

R^3 et R^4 représentent des substituants facultatifs sur le noyau B choisis indépendamment entre les groupes méthyle, éthyle, méthoxy, éthoxy, chloro, bromo, iodo, trifluorométhyle, cyano, nitro, trifluorométhoxy, 2-fluoréthoxy, 2,2,2-trifluoréthoxy, 3,3,3-trifluoropropoxy, hydroxy, hydroxyméthyle, 1-hydroxyéthyle et 2-hydroxyéthyle ;

T^3 est choisi entre les groupes méthyle, éthyle, propyle, butyle, isobutyle, sec-butyle, pentyle, hexyle, cyclopropyle, cyclopentyle, cyclohexyle, cyclopropylméthyle, cyclopentylméthyle, cyclohexylmé-

thyle, 2-cyclopentyléthyle, phényle, benzyle, 1-phényléthyle, 2-phényléthyle, fluorométhyle, trifluorométhyle, 2,2,2-trifluoréthyle, pentafluoréthyle, 2-méthoxyéthyle, 2-éthoxyéthyle, fluoro, chloro, bromo, iodo, méthoxy, éthoxy, propoxy, amino, méthylamino, éthylamino, butylamino, diméthylamino, diéthylamino et dipropylamino ;

T^4 est choisi entre l'hydrogène et les groupes méthyle, éthyle, propyle, méthoxy, éthoxy, propoxy, fluorométhyle, trifluorométhyle, 2,2,2-trifluoréthyle, pentafluoréthyle, carboxy, méthoxycarbonyle, éthoxycarbonyle, propoxycarbonyle, allyloxycarbonyle, 2-méthyl-2-propényloxycarbonyle, 3-méthyl-3-buténylоxycarbonyle, fluoro, chloro, bromo, iodo, cyano, nitro, carbamoyle, formyle, acétyle, butyryle, N-méthylcarbamoyle, N-éthylcarbamoyle, N,N-diméthylcarbamoyle, N,N-diéthylcarbamoyle, amino, méthylamino, éthylamino, butylamino, diméthylamino, diéthylamino, dipropylamino, et un groupe de formule $-A^1.B^1$ dans laquelle A^1 représente un groupe méthylène, éthylène, propylène, un groupe carbonyle ou une liaison directe et B^1 représente

(1) un groupe phényle non substitué ou phényle portant un ou deux substituants choisis indépendamment entre les groupes méthyle, éthyle, méthoxy, éthoxy, chloro, bromo, iodo, cyano, trifluorométhyle, nitro, hydroxy, carboxy, formamido, acétamido, propanamido, formyle, acétyle, butyryle, trifluorométhoxy, 2-fluoréthoxy, 2,2,2-trifluoréthoxy, 3,3,3-trifluoropropoxy, hydroxyméthyle, 1-hydroxyéthyle, 2-hydroxyéthyle, 2-méthoxyéthyle, 2-éthoxyéthyle, carbamoyle, N-méthylcarbamoyle et N-éthylcarbamoyle, N,N-diméthylcarbamoyle, N,N-diéthylcarbamoyle, sulfamoyle, N-méthylsulfamoyle, N-éthylsulfamoyle, N,N-diméthylsulfamoyle, N,N-diéthylsulfamoyle, méthoxycarbonyle, éthoxycarbonyle, propoxycarbonyle, méthanesul fonamido, éthanesulfonamido, méthylthio, éthylthio, méthylsulfinyle, éthylsulfinyle, méthylsulfonyle, éthylsulfonyle et 1H-tétrazole-5-yle;

ou

(2) un noyau hétérocyclique choisi entre les groupes thiényle, furyle, pyrrolyle, pyrrolidinyle, pyridyle, pipéridyle, imidazolyle, imidazolidinyle, pyrazolyle, pyrazolinyle, thiazolyle, thiazolinyle, oxazolyle, oxazolidinyle, pyrimidinyle, pyrazinyle, pyridazinyle, pipérazinyle, morpholinyle et thiomorpholinyle, ledit noyau portant facultativement un groupe méthyle ou éthyle ;

ou bien T^3 et T^4 forment conjointement un groupe triméthylène, tétraméthylène, pentaméthylène, 1-propénylène, 2-propénylène, 1-buténylène, 2-buténylène, 3-buténylène, 1-oxopropylidène, 3-oxopropylidène, 1-oxobutylidène ou 4-oxobutylidène, sous réserve que lorsque T^3 et T^4 forment conjointement l'un de ses vingt derniers groupes, T^2 soit choisi en outre entre n'importe lesquelles des valeurs définies précédemment pour T^4 ;

Y représente l'oxygène ou un groupe de formule -NRb- dans laquelle Rb représente l'hydrogène, un groupe méthyle, éthyle, formyle, acétyle, propanoyle ou benzoyle ;

E^1 représente l'hydrogène, un groupe méthyle, éthyle, propyle, butyle, isobutyle, sec-butyle, pentyle, hexyle ou trifluorométhyle ;

E^2 représente l'hydrogène, un groupe méthyle, éthyle, propyle, butyle, isobutyle, sec-butyle, pentyle, hexyle, fluoro, chloro, bromo, iodo, méthoxy, éthoxy, propoxy, trifluorométhyle, carboxy, méthoxycarbonyle, éthoxycarbonyle, propoxycarbonyle, allyloxycarbonyle, 2-méthyl-2-propényloxycarbonyle, 3-méthyl-3-buténylоxycarbonyle, cyano, nitro, formyle, acétyle, butyryle, méthylthio, éthylthio, méthylsulfinyle, éthylsulfinyle, méthylsulfonyle, éthylsulfonyle ou phénylsulfonyle ;

E^3 représente l'hydrogène, un groupe méthyle, éthyle, propyle, butyle, isobutyle, sec-butyle, pentyle, hexyle, fluoro, chloro, bromo, iodo, méthoxy, éthoxy, propoxy ou trifluorométhyle ;

E^4 et E^5 représentent des substituants facultatifs sur le groupe de jonction A choisis indépendamment entre les groupes méthyle, éthyle, fluorométhyle, trifluorométhyle, 2,2,2-trifluoréthyle, pentafluoréthyle, phényle, pyridyle, méthoxy, éthoxy, chloro, bromo, iodo, cyano, nitro, carboxy, méthoxycarbonyle, éthoxycarbonyle, propoxycarbonyle, allyloxycarbonyle, 2-méthyl-2-propényloxycarbonyle, 3-méthyl-3-buténylоxycarbonyle, carbamoyle, N-méthylcarbamoyle, N-éthylcarbamoyle, N,N-diméthylcarbamoyle, N,N-diéthylcarbamoyle, méthylthio, éthylthio, méthylsulfinyle, éthylsulfinyle, méthylsulfonyle, éthylsulfonyle, phénylthio, phénylsulfinyle, phénylsulfonyle, formyle, acétyle et butyryle ;

L^1 représente un groupe méthyle, éthyle, propyle, butyle, isobutyle, sec-butyle, pentyle ou hexyle ;

L^2 et L^3 sont choisis indépendamment entre l'hydrogène et les groupes méthyle et éthyle ;

X représente l'oxygène, le soufre ou un groupe de formule -NRc dans laquelle Rc représente l'hydrogène, un groupe méthyle ou éthyle ;

Ra est choisi entre l'hydrogène et les groupes méthyle, éthyle, méthoxy, éthoxy, chloro, bromo, iodo, trifluorométhyle, cyano et nitro ; et dans laquelle n'importe lequel desdits groupements phényle de R^1, R^2, T^1, T^2, T^3 ou E^2 peut être non substitué ou porter un ou deux substituants choisis indépendamment entre les groupes méthyle, éthyle, méthoxy, éthoxy, chloro, bromo, iodo, cyano et trifluorométhyle ; ou un de ses sels non toxiques.

3. Composé suivant la revendication 1 ou 2, mais excluant les composés dans lesquels l'un ou l'ensemble des groupes E^4 et E^5 est choisi entre des groupes phényle, pyridyle, carbamoyle, N-alkylcarbamoyle et di(N-alkyl)carbamoyle ayant jusqu'à 7 atomes de carbone, alkylthio en C_1 à C_4, alkylsulfinyle en C_1 à C_4, alkylsulfonyle en C_1 à C_4, phénylthio, phénylsulfinyle et phénylsulfonyle ; ou un de ses sels non toxiques.

4. Composé de formule I suivant la revendication 1, 2 ou 3, dans lequel Q représente un groupe répondant à la formule structurale partielle IIa.

5. Composé de formule I suivant la revendication 1, 2 ou 3, dans lequel Q représente un groupe répondant à la formule structurale partielle IIb.

6. Composé de formule I suivant la revendication 1, 2 ou 3, dans lequel Q représente un groupe répondant à la formule structurale partielle IIc.

7. Composé de formule I suivant la revendication 1, 2 ou 3, dans lequel Q représente un groupe répondant à la formule structurale partielle IId.

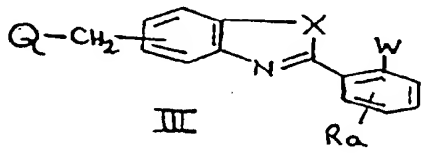
8. Composé de formule I suivant la revendication 1, 2 ou 3, dans lequel Q est choisi entre les groupes
2-(alkyle en C_1 à C_4)quinoléine-4-yloxy,
2-(alkyle en C_1 à C_4)-5,6,7,8-tétrahydroquinoléine-4-yloxy,
2,6-di-(alkyle en C_1 à C_4)-3-halogénopyrid-4-ylamino,
2,6-di-(alkyle en C_1 à C_4)-4-halogéno-1H-pyrrolo[3,2-c]pyrid-1-yle,
5,7-di-(alkyle en C_1 à C_4)-2-oxo-1,2-dihydro-1,6-naphthyridine-1-yle,
5,7-di-(alkyle en C_1 à C_4)-2-oxo-1,2,3,4-tétrahydro-1,6-naphthyridine-1-yle,
2-(alkyle en C_1 à C_4)-3H-imidazo[4,5-b]pyrid-3-yle, et
2,5,7-tri-(alkyle en C_1 à C_4)-3H-imidazo[4,5-b]pyrid-3-yle.

9. Composé de formule I suivant l'une quelconque des revendications précédentes, dans lequel X représente l'oxygène.

10. Composé de formule I, choisi entre :
la 2-éthyl-5,6,7,8-tétrahydro-4-[(2-(2-(1H-tétrazole-5-yl)phényl)-benzoxazole-5-yl)méthoxy]quinoléine et
la5,7-diméthyl-2-propyl-3-[(2-(2-(1H-tétrazole-5-yl)phényl)benzoxazole-5-yl)méthyl]-3H-imidazo[4,5-b]pyridine ; ou un de ses sels non toxiques.

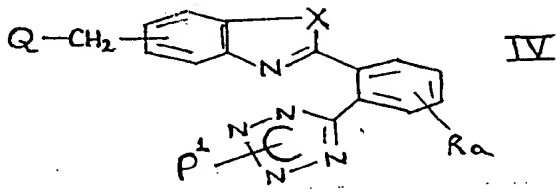
11. Sel suivant l'une quelconque des revendications précédentes, qui est choisi entre des sels formés avec des acides donnant des anions physiologiquement acceptables et des sels formés avec des bases donnant des cations physiologiquement acceptables.

12. Procédé de production d'un composé de formule I, ou d'un de ses sels non toxiques, suivant la revendication 1, qui est caractérisé en ce que :
(a) pour les composés dans lesquels Z représente un groupe carboxy, un dérivé d'acide carboxylique de formule III



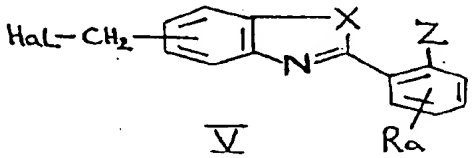
III

dans laquelle W représente un groupe carboxy protégé choisi entre des groupes (alkoxy en C_1 à C_6)-carbonyle, phénoxycarbonyle, benzyloxycarbonyle et carbamoyle, est transformé en un groupe carboxy ;
(b) pour les composés de formule I dans laquelle Z représente un groupe tétrazolyle, un composé de formule IV



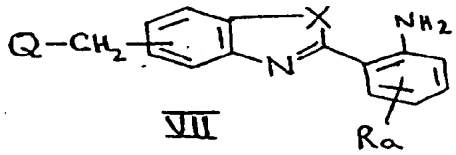
IV

dans laquelle P^1 représente un groupe protecteur fixé à l'atome d'azote du groupe tétrazolyle, est débarrassé de sa protection ;
(c) un composé de formule Q.H est alkylé avec un composé de formule V



V

dans laquelle Hal. représente un groupe partant convenable ; ou
(d) pour les composés de formule I dans laquelle Z représente un groupe de formule CF_3SO_2NH-, un composé de formule VII



VII

est amené à réagir avec l'anhydride trifluorométhanesulfonique ;

puis, lorsqu'un composé de formule I, dans laquelle Z représente un groupe 1H-tétrazole-5-yle est requis, un composé de formule I dans laquelle Z représente un groupe carboxy est transformé en le nitrile correspondant dans des conditions classiques, puis le nitrile est soumis à une réaction avec un azoture ;

puis, lorsque cela est nécessaire, n'importe quel groupe protecteur présent est éliminé ;

puis, lorsqu'un sel non toxique d'un composé de formule I est requis, ce sel est obtenu par réaction avec l'acide ou la base appropriée donnant un ion physiologiquement acceptable, ou par n'importe quel autre mode opératoire de formation de sel ; et

lorsqu'une forme optiquement active d'un composé de formule I est requise, un des procédés (a) à (d) précités est mis en oeuvre avec une matière de départ optiquement active, ou bien la forme racémique d'un composé de formule I est soumise à une résolution par réaction avec une forme optiquement active d'une base organique convenable, puis le mélange diastéréoisomère de sels ainsi obtenu est soumis à une séparation classique, et la forme optiquement active requise dudit composé de formule I est libérée par un traitement classique avec un acide ;

Q, X, Z et Ra ayant n'importe lesquelles des définitions mentionnées dans l'une quelconque des revendications 1 à 9, sauf spécification contraire.

13. Composition pharmaceutique qui comprend un composé de formule I, ou un de ses sels non toxiques, suivant l'une quelconque des revendications 1 à 11, en association avec un diluant ou support pharmaceutiquement acceptable.